Neuropsychiatric symptoms in patients with dementia in Norwegian nursing homes

- the course of the symptoms and the effect of discontinuation of psychotropic medication

Sverre Bergh

Faculty of medicine, University of Oslo

Department of Geriatric medicine, Oslo University Hospital

Centre for Old Age Psychiatry Research, Innlandet Hospital Trust

2011

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1310

ISBN 978-82-8264-340-5

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

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holder or the unit which grants the doctorate.

To my wife Torunn

og sem betur fer og sem betur fer þá fann ég þig hér

*"*þú komst við hjartað í mér*"*
Páll Óskar/Hjaltalin

Content

Acknowledgements

First of all I would like to thank my main supervisor Professor Knut Engedal. From the beginning of the project he has been inspiring and very supporting, always responding to my questions and comments in short time. He has generously shared his extensive knowledge from the field of geriatric psychiatry and research with me. I also want to thank my second supervisor Geir Selbæk, who has been enthusiastic about the project from the beginning and helped structuring and designing the project. Through their extensive network in the hospitals and nursing homes all over Norway, Knut and Geir have opened doors for me, making the project possible.

I have been employed at the Centre for Old Age Psychiatry Research at Innlandet Hospital Trust, and I would like to thank the manager Birger Lillesveen for the jovial atmosphere at the centre and for his support and believe in the project from the beginning. Thanks also to Birger and Geir for inviting me into the exciting world of research six years ago. I would like to thank the head of the Old Age Psychiatry department at Innlandet Hospital Trust, Susan Juel, and the former head of the department of psychiatry at Innlandet Hospital Trust, Solveig Brekke Skard, for their central role in building up the Centre for Old Age Psychiatry Research and for their support in the project. Great thanks to the staff at the Centre for Old Age Psychiatry Research at Innlandet Hospital Trust for their practical help with the project and for making the working day at the centre such fun. Especially, I would like to thank Elin Lillehovde for the close and fruitful cooperation with the DESEP study, Lisbeth Høgseth and Irene Røen for help with the data collection and Merethe Andreassen for designing and scanning the CRF used in the project. I would also thank the former and present manager and consultant of the Research Unit at Innlandet Hospital Trust for their interest in the project.

I am grateful for the job the principal investigators and study nurses at the 16 study centres have done in the DESEP study, including patients from 52 nursing homes in Norway. I want to thank the managers and staff at the nursing homes, the patients and their relatives for taking part in the project. Without their effort and interest in the project it could not have been realized. My hope is that the commitment the nursing homes put into the research, gave the staff increased knowledge and inspiration and improved the quality of care for the patients. I want to thank the statistician at Oslo University Hospital, Lien

Diep, the study monitor at Oslo University Hospital, Hege Øvergaard, and the monitor at Innlandet Hospital Trust, Cathrine Botten, for their help in planning and conducting the study and the statistical analysis. The staff at the Sykehusapoteket at Innlandet Hospital Trust Gjøvik has been very helpful in the randomization of patients and the distribution of study medication. I would also like to thank the members of the steering committee for the DESEP study for their contribution to the project.

Last, but not least, I want to thank my family. My mum Astrid and dad Kjell for encouraging me to work hard at school, for supporting me in my education and for being excellent role models as fellow humans and parents. My sister Ellen for supporting and taking care of me when needed and fighting me back when necessary. I would like to thank my family in law, for inviting me into their family as a son and brother. A huge thank to my wife Torunn, not just for being supportive when the progress in the project was slow and for paying attention and being interested in the research project, but for loving me all the years we have shared together. My children, Hulda, Birk and Sjur, for waiting patiently for me when I was away. Their friendship has literally been bought for buttons and glossy photographs from the airport. Thanks to my children for always sharing their happiness and joy with me, and making me remember that life is more than just work.

The project was financed by unrestricted grants from the Innlandet Hospital Trust, the South-Eastern Norway Regional Health Authority, The Research Council of Norway, Solveig og Johan P. Sommers stiftelse til fremme av klinisk psykiatrisk forskning, Demensforeningen in the Norwegian Health Association (Nasjonalforeningen for folkehelsen) and Lundbeck H/F. Without their contribution the project would not have been realized.

Abstract

Neuropsychiatric symptoms (NPS) are prevalent in dementia, and it has been estimated that up to 90% of people with dementia will experience NPS in the course of their dementia. Sometimes NPS in dementia are poorly diagnosed, and the effect of the treatment prescribed for the NPS has been poorly documented.

The aim of this thesis was to describe the prevalence, course and treatment of NPS in Norwegian nursing homes. We wanted to study whether NPS are transient or persistent. In addition, we wanted to investigate the effect of discontinuing treatment with antidepressants and antipsychotics on patients in Norwegian nursing homes with dementia and NPS. We conducted a small pilot discontinuation study, and a large double blind randomised controlled discontinuation trial (DB RCT). Previous DB RCT discontinuation studies of antipsychotics have shown that discontinuation of the medication has been beneficial for the patients, while the effect of the discontinuation of antidepressants in patients with dementia and NPS has not previously been studied in a DB RCT. To obtain good assessments of the cognitive function of the patients in the study, most of them having moderate or severe dementia, we translated the Severe Impairment Battery (SIB) into Norwegian and validated this instrument.

Four studies were conducted. In the validation study of the SIB 59 patients from three nursing homes in Hedmark and Oppland were included. In the study on the prevalence and the course of NPS in nursing homes, 210 patients from seven nursing homes in Hedmark and Oppland were included. In the pilot discontinuation study, 23 patients from seven nursing homes in Hedmark and Oppland were included, while in the DB RCT discontinuation study of antidepressants 128 patients from 52 nursing homes in 14 counties of Norway were included.

The Severe Impairment Battery (SIB) is a cognitive test for patients with moderate to severe dementia (minimum score 0 and maximum score 100). In the SIB validation study, three psychiatrists/doctors drafted the cognitive questionnaire into Norwegian before a psychiatrist made a final Norwegian translation from the three drafts. A colleague born in Newcastle, who has lived in Norway for several decades, translated the Norwegian version of the SIB back into English, and this version corresponded well with the original English version. The patients' cognition and degree of dementia were examined with the

SIB and the Clinical Dementia Rating scale (CDR), while the patients were diagnosed with dementia according to the International Classification of Diseases (ICD-10). A nurse and a doctor used the SIB to assess the patients within seven days of each other. The average SIB score was 72.10 points. In the reliability study Cronbach's alpha was 0.97, indicating a good internal reliability of the test. Spearman's rho correlation coefficient between the two testers was 0.85 for the total SIB score, and ranged between 0.46 and 0.76 for the sub-items of the test, which indicated a good inter-rater reliability. Scoring results on the SIB were compared with the CDR scores of patients. Spearman's rho correlation coefficient between the SIB score and the CDR score was 0.55. The groups of patients with CDR 1, 2 and 3 were significantly different from each other as measured by the SIB. By using Receiver Operating Characteristic (ROC) curve analysis we found that the SIB score of 87/88 best discriminated between CDR <2 and CDR 2, while the SIB score of 80/81 best discriminated between the CDR 2 and CDR 3 The study indicated that the Norwegian version of the SIB is reliable and valid, and can be used to evaluate cognition in patients with moderate and severe dementia.

In the study of the prevalence and the course of NPS, patients were examined at baseline (T0) and after four (T1) eight (T2), twelve (T3) and sixteen (T4) months with the Neuropsychiatric Inventory (NPI), CDR, the Mini-Mental State Examination (MMSE) and the Quality of Life in late-stage dementia (QUALID) scale. The NPI examines NPS, and we reported the prevalence and course of the NPS identified with the NPI. At baseline, the average age of the patients included was 84.9 years, 69.2% were female and the median length of stay in the nursing home was 673 days. The three most prevalent NPS were irritability, agitation/aggression and apathy (T0 and T1), irritability, agitation/aggression and disinhibition (T2 and T3) and depression, disinhibition and irritability (T4). Irritability had the highest cumulative prevalence (63.5%), followed by agitation/aggression (51.0%) and disinhibition (50.0%). In total, 91.7% of patients had at least one NPS during the 16 months period. Irritability (42.6%), disinhibition (37.8%) and depression (31.5%) had the highest cumulative incidence. The most persistent NPS were agitation/aggression, irritability and disinhibition (T0-T1) and (T1-T2), disinhibition, apathy and irritability (T2-T3) and hallucinations, depression and anxiety (T3-T4). The NPS with highest resolution rate were euphoria, appetite and eating disorders, and sleep and night-time behaviour disorders (T0-T1) and (T1-T2), appetite and eating disorders, hallucinations and delusions (T2-T3) and appetite and eating disorders, euphoria and apathy (T3-T4). The

conclusion of this study is that almost all patients included in this study have one or more NPS in the course of sixteen months, but individual symptoms fluctuate, which should affect the treatment which patients are given.

In the small pilot study where we investigated the effect of the discontinuation of antidepressants and antipsychotics, 23 patients with dementia, but without a depressive disorder, were included. Twelve patients used antipsychotics of different types and 11 patients used selective serotonin reuptake inhibitor (SSRI) antidepressants. Patients were examined at baseline with the CDR, the NPI, the Cornell Scale for Depression in Dementia (CSDD), a sub-scale of the Unified Parkinson's Disease Rating Scale (UPDRS), the SIB, the Lawton and Brody's Physical Self-Maintenance Scale (PSMS) and the Quality of Life-Alzheimer's Disease (QoL-AD) scale. At three, six and 12 weeks, patients were examined with the NPI and the UPDRS, and after 24 weeks the same assessment scales as at baseline were used. At inclusion the average age was 84.1 years and 91.3% were women. At three and six weeks, we found a small increase in the NPI and the UPDRS scores of patients in both groups, but at 12 and 24 weeks the scores on both scales were back to baseline levels. The SIB scores (cognition) at 24 weeks showed a slight decrease in the group who discontinued antidepressant medication and a small increase in the group who discontinued antipsychotics. The CSDD scores were unchanged in the antipsychotic group, but showed a small decrease in the antidepressant group. None of the results were statistically significant, but suggested that discontinuation of antidepressants and antipsychotics were safe in the patients with dementia and NPS, and could even be beneficial for the patients.

In the randomised double-blind RCT discontinuation study of antidepressants, the 128 patients were assessed with the same assessment tools as in the pilot study and the assessments were done at baseline and after four, seven, 13 and 25 weeks. The 128 patients used escitalopram, citalopram, sertraline or paroxetine at inclusion. In half of the patients the antidepressive medication was discontinued, while in the other half of the patients the medication was continued. The study was double blind and placebo-controlled, meaning that in patients who discontinued medication the antidepressant was substituted by placebo tablets or capsules identical in appearance to the study medication in those who continued with medication. Neither the patients, the relatives, employees at the nursing home or the study management knew which patients were in the

discontinuation group and which were in the active medication group, as randomisation and distribution of the study medication was made by the hospital pharmacy at Innlandet Hospital Trust, Gjøvik. Randomisation was by a computer-generated 1:1 allocation sequence. Sixty-three patients were allocated to the antidepressants discontinuation group (ADG), out of which 27 patients (42.9%) had to discontinue the study within 25 weeks. Sixty-five patients were allocated to the antidepressants continuation group (ACG), out of which 18 patients (27.7%) had to discontinue the study within 25 weeks. At baseline, the groups were comparable in terms of age, gender, NPI score, CSDD score and all the other measured variables. At 25 weeks, the ADG group had an increase of 2.53 points on the CSDD from 5.03 points while the ACG group had a decrease of -0.43 point from 5.89 points. The difference between the groups was statistically significant. A post hoc analysis showed that the difference in the total CSDD score between the groups were statistically significant different as early as at week 7 (visit 3). Measured with the NPI the ADG group had an increase of 5.93 points from 17.79 points while the ACG group had a decrease of -1.39 points from 17.63 points. When analysing the results with ANCOVA, and correcting for the baseline values of the CSDD, the difference between groups was still statistically significant. We analysed the mood sub-scores of the CSDD, based on a Norwegian factor analysis (Barca *et al.*, 2008), and the affective subscales of the NPI (NPI-depression + NPI Anxiety) to examine the mood symptoms of the patients. This analysis also showed statistically significant differences between the groups. For the other assessment tools – the CDR, the UPDRS, the QoL-AD and the PSMS – there were no statistically significant changes between baseline and 25 weeks. We concluded that discontinuation of antidepressants in patients who have dementia and NPS, but no depressive disorder, led to an increase in depressive symptoms.

Sammendrag

Nevropsykiatriske symptomer (NPS) er hyppig forekommende ved demens, og det er blitt estimert at opp mot 90 % av alle personer med demens vil oppleve NPS i løpet av sin demenssykdom. NPS ved demens er dessverre til dels dårlig diagnostisert, og effekten av behandlingen vi tilbyr ved NPS har vært dårlig dokumentert.

Målet med denne forskningen har vært å beskrive forekomst, forløp og behandling av NPS i norske sykehjem. Vi ønsket å undersøke hvilke nevropsykiatriske symptomer som var flyktige og hvilke symptomer som var vedvarende. I tillegg ønsket vi å undersøke effekten av å seponere antidepressiva hos pasienter på norske sykehjem med demens og NPS. Vi gjennomførte en liten pilotseponeringsstudie og en større dobbeltblind randomisert kontrollert seponeringsstudie (DB RCT). Tidligere DB RCT seponeringsstudier av antipsykotika har vist at seponeringen av medisinen har gagnet pasientene, mens effekten av å seponere antidepressiva hos pasienter med demens og NPS aldri tidligere har vært undersøkt i en DB RCT. For å ha et godt mål på den kognitive funksjonen hos pasientene i studien, som for det meste hadde moderat og alvorlig demens, oversatte vi the Severe Impairment Battery (SIB) til norsk, og validerte og reliabilitetstestet dette måleinstrumentet.

Fire studier ble gjennomført. I valideringsstudien av SIB ble 59 pasienter inkludert fra tre sykehjem i Hedmark og Oppland. I forekomst og forløpsstudien av NPS i sykehjem, ble 210 pasienter fra syv sykehjem i Hedmark og Oppland inkludert. I pilotseponeringsstudien ble 23 pasienter fra syv sykehjem i Hedmark og Oppland inkludert, og i DB RCT seponeringsstudien av antidepressiva ble 128 pasienter fra 52 sykehjem i 14 fylker av Norge inkludert.

The Severe Impairment Battery (SIB) er en kognitiv test som er tilrettelagt for pasienter med moderat til alvorlige demens. Minimum skåre på testen er 0 og maksimum skåre er 100. I valideringsstudien av SIB ble testen oversatt fra engelsk til norsk av tre psykiatere/leger før en fjerde psykiater laget en felles norsk versjon av de tre forslagene. En kollega født i Newcastle, som har bodd i Norge i flere tiår, oversatte den norske versjonen tilbake til engelsk, og denne versjonen var i overensstemmelse med den opprinnelige engelske versjonen. Pasientenes kognisjon og grad av demens ble undersøkt med SIB og the Clinical Dementia Rating scale (CDR), og pasientene ble diagnostisert

med demens i henhold til International Classification of Diseases (ICD-10). Testing med SIB ble gjort av en sykepleier og en lege med maksimum syv dagers mellomrom. Gjennomsnittlig SIB poengsum hos pasientene var 72,10 poeng. Cronbach's alfa var 0,97, som indikerer en god intern reliabilitet for testen. Spearman's rho korrelasjonskoeffisient mellom de to testerne var 0,85 for total SIB skåre, og varierte mellom 0,46 og 0,76 for underskårene i testen, noe som indikerte en god inter-rater reliabilitet. Skåringsresultatene på SIB ble sammenholdt med CDR skåre for pasientene. Spearman's rho korrelasjons koeffisient mellom SIB skåre og CDR var 0,55. Gruppene av pasienter med CDR 1, 2 og 3 var signifikant forskjellig fra hverandre målt med SIB. Ved hjelp av Receiver Operating Characteristic (ROC) kurve analyser fant vi at en SIB skåre på 87/88 best skilte mellom CDR<2 og CDR 2, mens en SIB skåre på 80/81 best skilte mellom CDR 2 og CDR 3. Studien indikerte at den norske versjonen av SIB er reliabel og valid, og kan benyttes til å evaluere kognisjonen hos pasienter med moderat og alvorlig grad av demens.

I forekomst- og forløpsstudien ble pasientene undersøkt ved baseline (T0) og etter fire (T1) åtte (T2), tolv (T3) og seksten(T4) måneder med Neuropsychiatric Inventory (NPI), CDR, Mini-Mental Status Evaluering (MMSE) og Quality of life in late-stage dementia (QUALID) skala. NPI undersøker NPS. Ved baseline var gjennomsnittsalder på de inkluderte pasientene 84,9 år, 69,2 % var kvinner og median lengde på sykehjemsoppholdet var 673 dager. De tre mest hyppige NPS ved de ulike måletidspunktene var irritabilitet, agitasjon og apati ved T0 og T1, irritabilitet, agitasjon og manglende hemninger ved T2 og T3, og depresjon, manglende hemninger og irritabilitet ved T4. Høyest kumulativ forekomst hadde irritabilitet (63.5 %), agitasjon (51.0 %) og manglende hemninger (50.0 %). Hele 91.7 % av pasientene hadde minst et NPS i løpet av 16 måneders perioden. Irritabilitet (42.6 %), manglende hemninger (37.8 %) og depresjon (31.5 %) hadde høyest kumulativ insidens. De mest vedvarende NPS var agitasjon, irritabilitet og manglende hemninger (T0–T1) og (T1–T2), manglende hemninger, apati og irritabilitet (T2–T3) og hallusinasjoner, depresjon og angst (T3–T4). De mest flyktige NPS var eufori, endringer i spisemønsteret og endret nattvaner (T0–T1) og (T1 – T2), endringer i spisemønsteret, hallusinasjoner og vrangforestillinger (T2–T3) og endringer i spisemønsteret, eufori og apati (T3–T4). Konklusjonen på denne undersøkelsen er at nesten alle pasienter innlagt på de sykehjem vi undersøkte har en eller flere NPS i løpet av seksten måneder, men de enkelte symptomene er flyktige, noe som burde ha innvirkning på behandlingen som pasientene tilbys.

I den lille pilotstudien hvor vi undersøkte effekten av seponering av antidepressiva og antipsykotika ble 23 pasienter med demens, uten en depressiv lidelse inkludert. I alt 12 pasienter brukte antipsykotika av forskjellige typer og 11 pasienter brukte antidepressiva av typen Selektive Serotonin Reopptak Inhibitor (SSRI). Pasientene ble undersøkt ved baseline med CDR, NPI, the Cornell Scale of Depression in Dementia (CSDD), en underskala av the Unified Parkinson's Disease Rating Scale (UPDRS), SIB, Lawton and Brody's Physical Self Maintenance Scale (PSMS) og Quality of Life- Alzheimer's Disease (QoL-AD). Ved tre, seks og 12 uker ble pasientene undersøkt med NPI og UPDRS, og etter 24 uker ble samme kartleggingsverktøy som ved baseline brukt. Ved inklusjon var gjennomsnittelig alder 84,1 år og 91,3 % var kvinner. Ved tre og seks uker fant vi en liten økning i NPI og UPDRS skåre hos pasientene i begge gruppene, men skåringene på begge skalaene gikk ved 12 og 24 uker tilbake igjen til utgangsverdien. SIB skåringene (kognisjon) viste ved 24 uker en liten nedgang i gruppen som seponerte antidepressiva og en liten økning i gruppen som seponerte antipsykotika. CSDD skåringene var uforandret i antipsykotika gruppa, men viste en nedgang i antidepressiva gruppa. Ingen av resultatene var statistisk signifikante, men antydet at seponering av antidepressiva og antipsykotika hos pasienter med demens og NPS var trygt, og til og med kunne være en fordel for pasientene.

I den dobbelblinde randomiserte seponeringsstudien av antidepressiva ble de 128 pasientene undersøkt med de samme kartleggingsverktøyene som i pilotstudien. Det ble gjort undersøkelser ved baseline og etter fire, sju, 13 og 25 uker. De 128 pasientene brukte enten escitalopram, citalopram, sertraline eller paroksetin ved inklusjon. Hos halvparten av pasientene ble medisinen seponert, mens den andre halvparten fortsatte med sin opprinnelige medisin. Studien var dobbelblind og placebokontrollert, dvs. at pasientene som fikk seponert antidepressiva fikk erstattet medikasjonen med placebotabletter eller kapsler med identisk utseende som den aktive medikasjonen. Verken pasienter, pårørende, ansatte på sykehjemmet eller studieledelsen visste hvilke pasienter som var i seponeringsgruppen eller hvilke som var i gruppen med aktiv medikasjon, da randomiseringen og utsending av studiemedikasjon ble gjort av sykehusapoteket på Gjøvik (og ble holdt hemmelig). Randomiseringen ble gjort med en datamaskin i henhold til en 1:1 randomiseringsliste. Seksti-tre pasienter fikk seponert antidepressiva (Antidepressiva Discontinuation Group - ADG), 27 (42.9 %) av dem måtte avbryte studien før 25 uker. Seksti-fem pasienter fortsatte med antidepressiva (Antidepressiva

Continuation Group - ACG), 18 (27.7 %) av dem måtte avbryte studien før 25 uker. Ved baseline var det ingen signifikante forskjeller mellom gruppene i forhold til alder, kjønn, NPI skåring, CSDD skåring eller alle andre målte variabler. Ved 25 uker hadde ADG-gruppen en økning på 2,53 poeng på CSDD fra 5,03 mens ACG-gruppen hadde en nedgang på -0,43 fra 5,89. Forskjellen mellom gruppene var statistisk signifikant. En post hoc analyse viste at forskjellen mellom gruppene målt med CSDD var statistisk signifikant forskjellig allerede etter 7 uker (besøk 3). Målt med NPI hadde ADG-gruppen en økning på 5,93 fra 17,79 mens ACG-gruppen hadde en nedgang på -1,39 fra 17,63. Ved en ANCOVA-analyse, der vi korrigerte for baselineverdier av CSDD, var forskjellen mellom gruppene fremdeles statistisk signifikante. Vi analyserte underskårer av CSDD og NPI for å se nærmere på effekten på de affektive symptomene. Også disse analysene viste statistisk signifikante forskjeller mellom gruppene. For de andre kartleggingsverktøyene; CDR, UPDRS, QoL-AD og Lawton og Brody ADL skjema (PSMS) fant vi ingen statistisk signifikante forskjeller mellom de to gruppene. Vi konkluderte at seponering av antidepressiva hos pasienter som har demens og NPS, men ingen depressiv lidelse, førte til en økning i depressive symptomer.

List of papers

I. Bergh S, Selbaek G, Engedal K. Reliability and validity of the Norwegian version of the Severe Impairment Battery (SIB). *Int J Geriatr Psychiatry* 2008; **23**: 896-902.

II. Bergh S, Engedal K, Roen I, Selbaek G. The course of neuropsychiatric symptoms in patients with dementia in Norwegian nursing homes. *Int Psychogeriatr* 2011; **23**: 1231-1239.

III. Bergh S, Engedal K. The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes: an open pilot study. *Int J Geriatr Psychiatry* 2008; **23**: 877-879.

IV. Bergh S, Selbaek G, Engedal K. A double blind, randomised placebo controlled discontinuation trial of antidepressants in persons with dementia and neuropsychiatric symptoms – the DESEP study. *Submitted 2011*

Abbreviations

AchEI	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical classification system
BPSD	Behavioural and Psychological Symptoms of Dementia
CDR	Clinical Dementia Rating scale
CSDD	Cornell Scale for Depression in Dementia
DB RCT	Double Blind Randomised Controlled Trial
DLB	Dementia with Lewy Bodies
DSM-IV TR	Diagnostic and Statistical Manual of mental disorders IV Text Revision
FTD	Frontotemporal Dementia
ICD-10	International Classification of Diseases 10^{th} edition
LOCF	Last-Observation-Carried-Forward method
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric Symptom
MMSE	Mini Mental State Examination
PDC-dAD	Provisional Diagnostic Criteria for Depression in Alzheimer's Disease
PSMS	Lawton and Brody's Physical Self-Maintenance Scale
QoL	Quality of Life
QoL-AD	Quality of Life-Alzheimer Disease
RCT	Randomised Controlled Trial
SIB	Severe Impairment Battery
SSRI	Selective Serotonin Reuptake Inhibitors
VaD	Vascular Dementia

1 Introduction

Although Alois Alzheimer's description of Auguste D and her disease, included in a lecture in November 1906, marks the beginning of dementia research, "dementia" is an ancient term first used more than 2,000 years ago. The Roman poet and philosopher Lucretius used the term "dementia" back in 50 B.C.E. in the sense of "being out of one's mind". At that time dementia was used to describe the condition of anyone who had lost their ability to reason, and was applied to patients with mental illness, infections involving the nervous system, and dementia experienced in old age. Dementia caused by old age was called "demences senilis", a term used in the first classification of mental diseases in 1838. Arnold Pick was a German neurologist and psychiatrist best known for identifying the syndrome named after him (Pick's disease), but in 1891 he used the term "dementia praecox" to describe patients with loss of cognitive function following a psychosis. Later "Dementia Praecox" was altered to schizophrenia, which is today's name for that disease.

Dementia is a syndrome including a decline in cognition to an extent that leads to functional impairment and a range of psychological and behavioural symptoms, such as hallucinations, delusion, anxiety, depression, agitation and disinhibition. The focus of research on dementia has been on symptoms, risk factors and treatment, both in nursing home patients and patients living at home.

The development of cognitive tests for patients with dementia has focused on tests for patients with mild to moderate cognitive impairment. Many of these cognitive tests, such as the Mini Mental State Examination (MMSE) and the Clock drawing (CDT) test are both valid and have excellent reliability, but they have a "floor effect", which means that the tests are not able to differentiate between patients below a certain threshold of cognitive impairment. The Clinical Dementia Rating scale (CDR) categorises the level of dementia into no dementia (CDR<1), mild dementia (CDR 1), moderate dementia (CDR 2) and severe dementia (CDR 3). Most of the patients with dementia in Norwegian nursing homes have moderate dementia (33.2%) or severe dementia (41.8%) (Selbaek *et al.*, 2007). To assess the changes in cognitive function in these patients more accurately, assessment tools for moderate to severe dementia have to be applied. The Severe Impairment Battery (SIB) was developed by Panisset and colleagues to overcome the floor effect (Panisset *et al.*, 1994), and can be applied among patients with moderate and severe

degree of dementia. We translated the SIB into Norwegian, validated the scale and tested it for reliability. This leads us to paper I of the thesis.

Neuropsychiatric Symptoms (NPS) are frequent in dementia. According to a previous study 81% of patients in Norwegian nursing homes have dementia, and 72% of patients with dementia have NPS (Selbaek *et al.*, 2007). The course of NPS fluctuates, and this has been demonstrated in several studies from different countries. The course of NPS in Norwegian nursing home patients has not been well studied. The only longitudinal study is at twelve month follow up study on a cohort of 1,163 patients (Selbaek *et al.*, 2008). Internationally, the study with the longest follow-up time on the course of NPS in nursing homes was made by Wetzels *et al*. in the Nederland, which included 290 nursing home residents with a follow-up of two years (Wetzels *et al.*, 2010b). We hypothesized that the NPS have a fluctuating course with rapid cycles and that a study of the course of NPS in Norwegian nursing homes with frequent assessments was necessary. This is covered in paper II of the thesis.

The treatments of NPS could be pharmacological and non-pharmacological. Studies on pharmacological treatment in Norwegian nursing homes have revealed that 75% of patients are prescribed psychotropic drugs (Selbaek *et al.*, 2007). Thirty-nine percent of the patients in the study by Selbaek et al were prescribed antidepressants, and 26% of the patients were prescribed antipsychotics (Selbaek *et al.*, 2007). In light of the lack of evidence for treating NPS and depression in dementia with antidepressants, we concluded that the prescription rate of antidepressants in Norwegian nursing homes was too high. We were curious to find out what the effect of antidepressant discontinuation in patients with dementia and NPS would be. An antidepressant discontinuation study in nursing homes would be the world's first DB RCT discontinuation study of antidepressants in patients with dementia and, no matter whether the results would support or discourage the discontinuation of antidepressants; the conclusion would be of interest to clinicians throughout the world. This is covered in papers III and IV of the thesis.

2 Background

2.1 Dementia

2.1.1 Definition, diagnosis, prevalence and risk factors

Dementia is not one illness or disease, but a clinical syndrome or a group of symptoms characterised by a decline in cognitive function to an extent that leads to functional impairment, as well as the occurrence of behavioural and psychological symptoms. Decline in cognition is the main symptom in most of the patients with dementia, although the first symptom of some of the dementia diseases is a behavioural or psychological symptom. Diagnosis of dementia is in two steps. Step one is to diagnose the dementia syndrome; step two is to diagnose the specific disease causing the dementia syndrome. Dementia is normally diagnosed according to the criteria of the International Classification of Diseases, version 10 (ICD-10), published by the World Health Organisation (WHO) in 1993, or the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, (DSM-IV-TR), published by the American Psychiatric Association (APA) in 1994. The ICD-10 is in use in Norway, and textbox 1 displays the ICD-10 research criteria for dementia. Although a large number of diseases may cause dementia, 95% of the dementias are caused by five diseases. The most frequent cause of dementia is Alzheimer's Disease (AD), followed by Vascular Dementia (VaD), Dementia with Lewy Bodies (DLB), Frontotemporal Dementia (FTD), and dementia caused by excessive use of alcohol. Dementia is directly caused by neuronal dysfunction of the brain, and neuronal degeneration is found in AD, DLB and FTD. Depositions of extracellular β-amyloid plaques and neurofibrillary tangles intracellular in neurons in the brain are found in AD. In DLB, Lewy bodies are found in the brain stem and also in cortical areas. FTD can be caused by a variety of disorders, which lead to cell death in frontal and temporal lobes of the brain. Depositions of Pick's cells are seen in Pick's disease, but most often other causes of neurodegeneration are seen in FTD. A cerebrovascular infarct, caused by a thrombosis with loss of blood flow to brain areas or a hemorrhagic stroke, will cause cell death in neurons in VaD. In alcoholic dementia a combination of thiamine malnutrition and a neurotoxic effect of the alcohol on brain cells contributes to the dementia (Joyce, 1994).

Textbox 1

Definition of the dementia syndrome, according to the ICD-10 research criteria

I. Evidence of each of the following:

   a. A decline in memory. The decline should be objectively verified.
   b. A decline in other cognitive abilities characterised by deterioration in judgement and thinking, such as planning and organising, and in the general processing of information.

   - *Mild.* The decline in cognitive abilities causes impaired performance in daily living, but not to a degree making the individual dependent on others.
   - *Moderate.* The decline in cognitive abilities makes the individual unable to function without the assistance of another in daily living.
   - *Severe.* The decline is characterised by an absence, or virtual absence, of intelligible ideation.

II. Preserved awareness of the environment (i.e. absence of clouding of consciousness). When there are superimposed episodes of delirium the diagnosis of dementia should be deferred.

III. A decline in emotional control or motivation, or a change in social behaviour, manifest as at least one of the following:
   a. Emotional lability;
   b. Irritability;
   c. Apathy;
   d. Coarsening of social behaviour.

IV. For a confident clinical diagnosis, G1 should have been present for at least six months; if the period since the manifest onset is shorter, the diagnosis can only be tentative.

The differences in the clinical pictures of different types of dementia are best seen early in the course of the disease. Later the clinical picture is blurred and a precise diagnosis is difficult to make. In patients with AD the dementia in most cases presents with a memory decline as the first sign, but also dysfunction in other cognitive functions, such as attention, problem solving and orientation occurs. In FTD the memory of the patients is normally intact in the early stages. Instead these patients have decreased executive function, inattention, lack of motivation and socially aberrant behaviour as the first presenting symptoms. AD, DLB and FTD exhibit a gradual progression of the disease.

Patients with DLB have parkinsonism, visual hallucinations and fluctuation in cognitive function as markers of the disease, and two of the three symptoms should be present for a diagnosis of DLB to be made. Patients with VaD are a heterogeneous group, whose disease can be classified into post-stroke dementia, vascular dementia (cortical and sub-cortical multi-infarct dementia, hypoperfusion and haemorrhagic dementia), mixed AD/VaD and vascular MCI (O'Brien *et al.*, 2003). Some patients with VaD go through an acute onset of symptoms at first (F01.0, VaD with acute onset) related to the cerebrovascular incident, while other patients have a gradual onset (F01.1, multi-infarct dementia). Structural images of their brains show vascular pathology, but the dementia symptoms will vary according to where in the brain the cerebral infarcts are located. Dementia caused by excessive alcohol use is recognisable by a decline in memory, confabulation and decreased motivation, but some patients demonstrate frontal pathology such as disinhibition. Secondary dementia caused by other diseases, such as thyroid dysfunction, infections, subdural hematomas and brain tumours are rare but should be excluded by a diagnostic assessment.

There are no exact prevalence numbers for the different dementia diagnoses in the literature, but a meta-analysis suggests that 60-70% of dementias are caused by AD, 20-30% are caused by VaD and the rest are caused by other types of dementias (Lobo *et al.*, 2000). The introduction of the new criteria for DLB (McKeith *et al.*, 2005) has focused attention on the disease, and in a Norwegian study of patients with mild dementia referred to geriatric and old-age psychiatric out-clinics the prevalence of DLB was 20% (Aarsland *et al.*, 2008). Dementia is a chronic condition that eventually leads to the death of the patient (Sachs *et al.*, 2011).

The only population-based prevalence studies on dementia in Norway were done twenty-five years ago, and are from Oslo (Engedal *et al.*, 1988;Engedal, 1993). In this study the prevalence of dementia in elderly aged 75 years and above and living in their own home was 10.5% (severe dementia 3.8% and mild dementia 6.7%) (Engedal *et al.*, 1988). For patients living in nursing home the prevalence of dementia was 71.6% (Engedal, 1993). In a study of 4,736 elderly persons receiving in-home care or living in nursing homes in Norway, 24.8% of the persons living at home and 74.9% of nursing-home patients had dementia (Nygaard *et al.*, 1987). A study on the prevalence of dementia in a non-representative sample of Norwegian nursing homes has been conducted, showing a

prevalence of dementia in nursing homes of 82% (Nygaard *et al.*, 2000). When estimating the number of patients with dementia in Norway we have to include information from studies in related countries and extrapolate the numbers (Harvey *et al.*, 2003;Ott *et al.*, 1998;Ott *et al.*, 1995). Table 1 shows the prevalence of dementia in Oslo, Rotterdam and England.

Table 1. Prevalence of dementia in Norway extrapolated from other studies

Age (years)	London	Rotterdam	Oslo	Estimates of number of persons with dementia in Norway
45-64	0.08 – 0.12%			900-1300
65-69		0.9%		1 468
70-74		2.1%		3 369
75-79		6.1%	10.1%	9 198
80-84		17.6%	16.7%	20 115
85-89		31.7%	26.2%	19 127
90+		40.7%	28.3%	10 920
Total				65 000

Adapted from (Engedal and Haugen, 2004)

It is estimated that 24.3 million people worldwide have dementia, and the number is expected to increase to approximately 81.1 million by 2040 (Ferri *et al.*, 2005). The one-year incidence of dementia worldwide is 4.6 million. Most of the patients with dementia are living in the developing countries, which have the highest incidence rate as well.

The economic costs for dementia are difficult to estimate. According to a report from the World Health Organisation (WHO), assessing disability with the Global Burden of Disease, dementia is the disease which contributes to most years of disability (11.2%), followed by stroke, musculoskeletal disorders and cardiovascular disease (World Health Organization, 2003).

Major risk factors for dementia are old age (Lobo *et al.*, 2000), vascular risk factors and genetic polymorphism. Vascular risk factors such as high blood pressure, Diabetes Mellitus and hypercholesterolemia have been intensively studied, indicating a plausible positive association (Skoog *et al.*, 1996;Ott *et al.*, 1999;Kivipelto *et al.*, 2002). Nevertheless, double blinded randomised placebo controlled trials (DB RCT) intervening on the vascular risk factor did not decrease the risk of dementia (Ligthart *et al.*, 2010). Lately the attention has been drawn to genetic research, and the strongest correlation is found between persons being a homozygotic APOE-ε4 carrier and Alzheimer's disease (Farrer *et al.*, 1997), although there is evidence for APOE-ε4 being a risk factor for VaD as well (Jones *et al.*, 2011). Large genetic studies with more than 5000 included AD patients and controls have found associations between AD and other loci as the ApoJ, PICALM and CR1 (Harold *et al.*, 2009;Lambert *et al.*, 2009).

Recent studies have concluded that a socially active life, physical activity, a healthy diet, and mentally and intellectually stimulating activities are protective factors against dementia (Kivipelto and Solomon, 2008;Fratiglioni and Qiu, 2009;Fratiglioni *et al.*, 2004). A recent meta-analysis concluded that physical activity was protective against VaD (Aarsland *et al.*, 2010).

2.1.2 Cognitive Assessment scales and diagnostic procedure

A wide selection of cognitive tests is available for the assessment of patients with suspected dementia. Some tests are screening tests for declining cognitive function; some tests are for the examination of global cognitive function, while others are for the assessment of specific cognitive functions. The Mini Mental State Examination is one of the world's most used screening tests for cognitive dysfunction (Folstein *et al.*, 1975), and is useful in differentiating between persons with dementia of moderate or severe degree and persons without dementia. However, the MMSE does not differentiate very well between persons with mild cognitive impairment (MCI) and those with a mild degree of dementia (Edhag and Norlund, 2006;SBU, 2008). The clock-drawing test is a screening test for executive function and visuospatial capacity (Sunderland *et al.*, 1989). The Trail-Making Test A (TMT-A) and Trail-Making Test B (TMT-B) are assessment scales which evaluate attention, speed and mental flexibility (Reitan RM, 1955). The Ten Word recall test from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) battery of tests is a visual and verbal memory test, and other parts of the CERAD battery

of neuropsychological tests are the Boston naming test for aphasia and Constructional Praxis. The Controlled Oral Word Association Test (COWAT) is a verbal fluency test. The Rey Auditory Verbal Learning Test (AVLT), California Verbal Learning Test (CVLT) and the Kendrick Object Learning Test are other examples of memory tests (Morris *et al.*, 1989;Kendrick DC *et al.*, 1979;Rey A, 1964;Delis *et al.*, 1988).

Cognitive assessment in the later stages of dementia

In the later stages of dementia the cognitive tests used in investigations in the early stages do not work well to measure the degree of cognitive impairment, due to floor effects. Therefore, other methods are used. One way to measure degree of cognition is to obtain proxy information from carers or relatives and use this information together with information from interviews with the patients to rate the degree of dementia. The Clinical Dementia Rating Scale (CDR) is a six-item questionnaire (memory, orientation, judgement and problem solving, community affairs, homes and hobbies and personal care) (Hughes *et al.*, 1982), where the patients' degree of dementia is scored based on all available information. The CDR categorises the severity of the dementia as no dementia (CDR=0), possible dementia (CDR=0.5), mild (CDR=1), moderate (CDR=2) or severe dementia (CDR=3). The Global Deterioration Scale for the Assessment of Primary Degenerative Dementia (GDS) categorises the dementia into seven stages according to the cognitive decline (Reisberg *et al.*, 1982), while the Functional Assessment Staging Test (FAST) consists of 16 stages and sub-stages (Reisberg, 1988). The Severe Impairment Battery (SIB) is a cognitive test with 51 items (minimum score zero, maximum score 100), especially developed for patients with moderate and severe dementia (Saxton and Swihart, 1989). The SIB consists of both multiple choice questions and tests for practical skills, which makes the questionnaire feasible for patients with moderate and severe dementia.

Other examinations

A diagnostic investigation of patients with suspected cognitive decline or dementia should, in addition to the evaluation of cognition, include a structural and in many cases also a functional imaging of the brain, as well as blood tests. Biological tests will contribute to the investigation both to find treatable causes of dementia, such as brain

tumours and pathological thyroid function, but also in the differentiation of dementia types.

Conventional Computer Tomography (CT) of the brain in patients with AD shows loss of brain substance in the temporal and parietal parts of the brain cortex, but the changes are not visible in all the patients with a very mild degree of AD. Magnetic Resonance Imaging (MRI) will, as the CT, show structural changes in the brain, but is more sensitive to show decreased volumes of the hippocampus area in patients with AD, DLB, FTD and VaD (Firbank *et al.*, 2011;Barber *et al.*, 2000;Galton *et al.*, 2001). Ppatients with AD have a bigger reduction in their hippocampus volume than patients with VaD and DLB (Burton *et al.*, 2009). Both MRI and CT will be useful in diagnosing VaD by detecting cerebrovascular infarcts. Patients with FTD have loss of brain substance in the frontal and temporal area of the brain cortex which is often visible on MRI scans (but not always in the very mild cases).

Functional imaging of the brain by Single-Photon Emission-Computed Tomography (SPECT) shows decreased blood flow in the frontal and temporal areas of the brain in FTD and in the temporal and parietal area in AD, and may be useful to distinguish FTD and AD more accurately, (Ballard *et al.*, 2011b). Positron emission tomography (PET) is a widely used method for functional imaging of tissue, not only in the brain. If the biologically active molecule chosen for PET is an analogue of glucose (FDG), the concentrations of tracer that appear on the image give the metabolic activity of the tissue. The FDG-PET scan of the brain is useful in discriminating AD from other dementias (Berti *et al.*, 2011). The newly developed method of amyloid imaging with pathology specific Aβ-PET will improve early detection of AD (Mosconi *et al.*, 2010). Elevated levels of amyloid plaque in brain tissue, assessed with PET-scans, are found in patients with AD and DLB compared to controls and patients with FTD, and the amyloid deposition is especially prevalent early in the course of the disease (Quigley *et al.*, 2011). In AD lower concentration of beta-amyloid and higher concentration of phosphorylated tau is found in the cerebrospinal fluid (CSF), and analyses of spinal fluid may be helpful in the diagnostic investigation (Hansson *et al.*, 2006).

2.1.3 Treatment

At the moment there is no cure for any types of dementia, and the current available medical treatment for dementia, cognitive enhancers, can only modify the symptoms of the dementia in patients with AD, Parkinson's disease with Dementia (PDD) and DLB, VaD and mixed AD/VaD. Two classes of cognitive enhancers are licensed for use in Norway, but neither the acetylcholinesterase inhibitors (AchEI) nor memantine have demonstrated more than a modest effect on cognition, performance of ADL or a clinical global impression of change (McShane *et al.*, 2006;Birks and Harvey, 2003). The effect of AchEI on NPS has been studied on several occasions, but the results are contradictory. Best evidence is for the effect of AchEI in reducing apathy, depression and aberrant motor behaviour (Gauthier *et al.*, 2010). One study has reported a reduction in agitation in patients with AD in nursing homes using donepezil (Tariot *et al.*, 2001). In recent decades a variety of research groups have worked to develop and study the effects of active immunisation as a therapy to reduce amyloid plaque in transgenic mice. The trials have been successful in reducing the amyloid deposit in mice brains, but the memory did not improve (Morgan, 2011). Passive immunisation with antibodies has been tested out in patients with Alzheimer's Disease, and has led to amyloid plaque clearance, but no improvement in cognition (Morgan, 2011). Immunisation has possible dangerous side effects, such as microhaemorrhages, encephalitis and vasogenic intracranial oedemas.

2.2 Neuropsychiatric Symptoms

2.2.1 Definitions and diagnosis

The recognised symptom of dementia is cognitive impairment and especially a decline in memory. However, the accompanying symptoms of dementia such as apathy, depression, agitation and delusion, are often more devastating and create more discomfort for the patients and cause more distress for the carers than the cognitive deficit. Defining the group of behavioural and psychological symptoms into a specific syndrome has been challenging, and different names for this group of symptoms have been applied. Due to the diversity of the symptoms, it has been difficult to agree upon one term that describes the whole group of symptoms. As this group of symptoms are symptoms associated with dementia, but different from cognitive dysfunction, "non-cognitive symptoms of dementia" has been proposed as a term for the group of symptoms. Other terms, such as

"behavioural disturbances" and "challenging behaviour", refer to the altered behaviour (such as apathy, agitation or aggression), while "neuropsychiatric symptoms" refer to the more psychological symptoms, for example delusions, hallucinations, depression and anxiety. The term "Behavioural and Psychological Symptoms of Dementia" (BPSD) was first presented at the International Psychogeriatric Association's (IPA) Initial Consensus Conference on BPSD in 1996, and BPSD was defined as "Signs and symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia" (Finkel *et al.*, 1996). The IPA established a task force to define the concept, presented at the Update Consensus Conference, entitled "Behavioural and Psychological Symptoms of Dementia (BPSD): A Clinical and Research Update", held in May 1999. Over the next decade "BPSD" was frequently used to describe the group of symptoms. The problems of aggregating several distinct symptoms into one syndrome or concept soon were apparent, and criticism strengthened. Problems escalated even more when clinical trials on the treatment for BPSD often used the total score on assessment scales for BPSD when evaluating efficacy of psychotropic medications. It has been argued that the symptoms of BPSD should be treated individually, and not as a syndrome. In recent years more and more researchers and clinicians have used the term "neuropsychiatric symptoms of dementia (NPS)", or even divided the group of symptoms into distinct individual symptoms, such as depression in dementia. For the rest of this thesis I will use the term "NPS" when talking about behavioural or psychological symptoms of dementia. Some of the individual neuropsychiatric symptoms have naturally been classified into sub-syndromes, e.g. psychosis consisting of delusion and hallucinations. Factor analyses of the assessment scales for NPS have supported the aggregation of single symptoms of NPS into sub-syndromes.

2.2.2 Clinical presentation

The definition and classification of the individual neuropsychiatric symptoms are important to ensure that we all discuss the same symptoms, but the classification may be challenging. For most of the NPS neither the ICD-10 nor the DSM-IV provides good and reliable definitions for NPS, and there are no specific diagnoses for NPS. The definition of individual NPS is mostly based on the various assessment scales that are used to classify and quantify NPS. In any case, some individual symptoms or signs of NPS, or specific sub-syndromes, do need specific consideration.

2.2.2.1 Delusion

Delusions in patients with dementia are often simple in their presentation. Paranoid types of delusion are common, best described as fear of being robbed, fear that their spouse is cheating on them or fear of being persecuted. More complex and bizarre delusions, as may be seen in patients with schizophrenia, are seldom seen in patients with dementia (Jeste and Finkel, 2000). Delusions is frequent in AD.

2.2.2.2 Hallucinations

Visual hallucinations are by far the most common type of hallucinations in patients with dementia, both in patients with AD and in patients with DLB (Jeste and Finkel, 2000). In patients with DLB visual hallucinations are frequent. The hallucinations in DLB are recurrent in nature, are usually present early in the disease and are persistent throughout course of the disease (Weisman and McKeith, 2007).

Misidentification is common in patients with dementia, and should be distinguished from delusions and hallucinations. They are usually visual in their nature, e.g. misidentification of close relatives or misidentification of the patients' own mirror reflection.

2.2.2.3 Depressive symptoms

Depressive symptoms occur frequently in dementia, but should be distinguished from a depressive disorder in patients with dementia. Depressive disorders are defined in the ICD-10, and the same diagnostic criteria are applied to patients with dementia as to patients without dementia. Diagnosis of a depressive disorder in patients with dementia is difficult, and a discussion of symptoms and assessment scales will be covered in chapter 2.3. It is important for the treatment of patients with dementia to differentiate a diagnosis of a depressive disorder in dementia from depressive symptoms in dementia, as the choice of treatment depends on this difference. The cut off between a depressive disorder in dementia and depressive symptoms in dementia is unclear and precise diagnosis is challenging, due to variety in the expression of symptoms, overlap between dementia and depression symptoms, as well as the patients' communications and language problems. Depressive symptoms are frequent in VaD and DLB.

2.2.2.4 Anxiety

Patients with dementia are often concerned about the future and worry about forthcoming events and plans. As a natural reaction to their loss of memory and cognitive decline, the patients lose track of their belongings, and are then concerned that their belongings may be lost. There is no exact definition of anxiety in dementia, although some argue for using DSM-IV or ICD-10 criteria for anxiety. One important consideration is how anxiety in patients with dementia is expressed, and it has been suggested that other NPS, such as agitation, irritability and aggression, could be interpreted as signs of anxiety (Clive-Reed and Gellis, 2011). This broadened definition of anxiety in dementia that some researchers have adopted is also reflected in the prevalence number for anxiety in dementia, which varies from 25 to 70% (Ballard *et al.*, 2000;Teri *et al.*, 1999).

2.2.2.5 Apathy

Apathy in dementia is one of the most prevalent NPS, and causes distress for the patients and reduces their Quality of Life. Apathy may be a sign of lack of internal motivation or a sign of behavioural inactivity (Brodaty and Burns, 2011). Several definitions of apathy in dementia have been formulated, but most of them include points such as diminished response to reward and lack of goal-directed behaviour (Brown and Pluck, 2000). Apathy is frequent in AD, FTD and VaD.

2.2.2.6 Agitation

Agitation in dementia is often recognised as wandering, restlessness, repetitive behaviour, attention seeking, screaming, plucking and pacing. A widely used definition is the classification of agitation by Cohen-Mansfield as aggressive behaviour, physically nonaggressive behaviour and verbally agitated behaviour (Cohen-Mansfield *et al.*, 1989).

2.2.2.7 Irritability/aggression

Physically aggressive behaviour in dementia is widely seen, and causes a lot of distress for the patients, the carers and the relatives. A wide definition of physical aggression is given by Patel and Hope: “an overt act involving delivery of a noxious stimulus to another person which was clearly not accidental” (Patel and Hope, 1992).

2.2.2.8 Disinhibition

Disinhibition is one of the core symptoms in FTD, leading to impulsive or inappropriate behaviour, swearing, and outbursts of frustration or lack of social tact. Patients may also lack inhibition with regard to handling their finances, shop lifting or aberrant sexual behaviour.

2.2.3 Assessment scales

There are methodological challenges related to the assessment scales for NPS. Due to the patients' cognitive decline, loss of insight and decline in language and communication abilities most of the patients are unable to describe the symptoms themselves. Hence, several assessment scales for NPS are based on observations made by either the carers or the relatives, but the observation-based assessment scales rely on different aspects of the patient–carer relationship as well as the carer's personal experiences and attitude to the patient. The challenge has been to develop assessment scales that are both valid and reliable. The validity of the questionnaire has to be strong, that is that the assessment scales are assessing what they are meant to assess. Further, the assessment scales should assess the patients in a similar way if rated by two or more persons (inter-rater reliability), as well as at different time points (test–retest reliability). Assessment scales for neuropsychiatric symptoms may be global (assessing different symptoms within the NPS spectrum) or a specific scale especially developed to rate one single NPS. The Neuropsychiatric Inventory (NPI) is a well-known global assessment scale widely used in both research and in clinical practice (Cummings *et al.*, 1994). The NPI originally consisted of 10 different items: delusions, hallucinations, depression/dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy and aberrant motor activity. Later, two neurovegetative items, sleep and night-time behaviour disorders, and appetite and eating disorders, were added to the NPI and this version is often referred to as the NPI-12 as opposed to the original NPI-10 version (Cummings, 1997). Each symptom in the NPI is first rated as present or not during the last four weeks, and if present the frequency is rated on a scale from 1 to 4 where 4 is most frequent, while the severity of the symptom is rated on a scale from 1 to 3 where 3 is most severe. Each symptom is rated alone, without taking into account the other NPS. The frequency score and the severity score are multiplied together and thereafter the scores of all 12 symptoms are added together giving a maximum score of 144. A score above three on an individual NPS is

regarded as a clinically significant symptom (Steinberg *et al.*, 2004). As the NPI consists of symptoms that are phenomenologically different, the total score on the NPI is not always the best way to quantify the burden of NPS on the patients. Several studies have, therefore, through a factor analysis, divided the NPI scale into sub-syndromes (Aalten *et al.*, 2003;Selbaek and Engedal, 2011).

Another widely used global assessment scale for NPS is the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) (Reisberg *et al.*, 1996;Reisberg *et al.*, 1987). The BEHAVE-AD was developed in 1987 as an attempt to overcome the problem of the rating scales of NPS used at that time, where assessments of cognition, functionality and NPS were done on the same assessments scale (Reisberg *et al.*, 1996). The motivation for the development of a questionnaire solely assessing NPS has to be seen in the light of the definition of the BPSD at that time. The 25 items of the BEHAVE-AD are grouped into seven major categories (Paranoid and delusional ideation, Hallucinations, Activity disturbances, Aggressiveness, Diurnal rhythm disturbances, Affective disturbances and Anxieties and phobias). The severity of each symptom is scored on a 4-point scale, where 0 = not present, 1 = present, 2 = present, generally with an emotional component, and 3 = present, generally with an emotional and physical component. In addition the BEHAVE-AD contains a 4-point global assessment of the overall magnitude of the NPS.

For individual symptoms, such as depression, anxiety and agitation, assessment scales tailored for specific symptoms have been developed. Assessment scales for depression are the Cornell Scale of Depression in Dementia (CSDD) (Alexopoulos *et al.*, 1988a), the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1982), the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Among those scales the only ad proxy based scale is the CSDD, which for this reason is the most feasible assessment scale for depression in patients with dementia.

Agitation has been of particular interest to researchers. The Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield, 1996) is a questionnaire for agitation in dementia. and the Brief Agitation Rating Scale (BARS) is a sub-scale of the CMAI (Finkel *et al.*, 1993).

2.2.4 NPS and different dementia types

The differences in symptoms and signs between different types of dementia are largest at the start of the various dementia disorders. In the severe stage, regardless of which dementia disorder is present, most patients experience more or less all the symptoms of dementia and the clinical picture is blurred.

2.2.4.1 Alzheimer's disease

In AD NPS are frequently found, especially in the severe stages of the disease, and patients are characteristically identified with anxiety, apathy and depression (Spalletta *et al.*, 2010). A recent review concluded, by using weighted means from three studies, that apathy (55.5%), depression (45.9%) and anxiety (42.0%) were the three most prevalent NPS in AD (Gauthier *et al.*, 2010). While the prevalence rate of depression is stable across the severity of the dementia, prevalence rates for apathy increases with increasing severity. If psychotic symptoms are present delusions are more prevalent than hallucinations.

2.2.4.2 Dementia with Lewy Body (DLB)/Parkinson's disease with dementia (PDD)

DLB is associated with hallucination, delusion, depression, irritability and aggression. In a Norwegian prospective study over twelve years almost 60% of the patients with DLB had developed psychosis (Forsaa *et al.*, 2010). Hallucination in the DLB is usually of the visual type, and is regarded as a mark of the disease and is one of the criteria for DLB (McKeith *et al.*, 1996). As many as 50 to 80% of patients with DLB and 78% of patients with Parkinson's disease and dementia have visual hallucinations (Harding *et al.*, 2002;Gold, 2009). Disinhibition is frequent in DLB, found in 65% of the patients (Engelborghs *et al.*, 2005), while in a study with 339 patients with DLB, 63.1% of the patients had sleep disturbances assessed with NPI-Q (Bliwise *et al.*, 2011). Significantly more sleep disturbances were found in patients with dementia (71%) than in patients without dementia (55.7%), and most sleep disturbances were found in patients with DLB (Rongve *et al.*, 2010). Depression is more prevalent in patients with DLB/PDD than in patients with AD (Fritze *et al.*, 2011).

2.2.4.3 Vascular Dementia (VaD)

Patients with vascular dementia are a heterogeneous group, ranging from patients with one large single infarct to patients with sub cortical ischemic cerebrovascular dementia.

Depression, emotional lability and apathy is common in VaD, especially depression, while psychosis is less prevalent in VaD than other types of dementias (O'Brien, 2003). Depression and anxiety are found to be equally common in VaD as in AD (Ballard *et al.*, 2000).

2.2.4.4 Frontotemporal Dementia (FTD)

Patients with FTD seldom experience cognitive decline at the beginning of their disease, while NPS such as apathy, disinhibition, irritability and aberrant social behaviour dominate their dementia (Engelborghs *et al.*, 2005). Psychotic symptoms are very rare in patients with FTD.

2.2.4.5 Dementia due to excessive alcohol use

Patients with dementia due to excessive alcohol use usually present with apathy and loss of attention, in addition to confabulation. Some of the patients have disinhibition, if they have damage in the frontal lobes of their brain.

2.2.5 Prevalence of NPS

Prevalence rates of NPS are available from studies from different geographical areas and from different settings. Estimates of the overall prevalence of NPS for patients with dementia, defined as expressing at least one individual NPS at a given time, range from 25 to 80% according to the cohort studied. This variation in prevalence rates is most likely caused by methodological issues, such as differences in the cohorts studied, both in level of care, diagnosis of dementia, time frame of data collection, assessment tools and threshold for defining a symptom as present. The prevalence of some individual NPS differs according to the severity of the dementia and type of dementia disease, while the prevalence of other individual NPS are stable across type of dementia and severity. This is reflected in different prevalence rates in patients living at home and in institutions.

2.2.5.1 Population based studies

Population based studies (recruiting patients from the community and not through clinical settings) are important to the description of the prevalence of NPS, in that they reduce the bias found in studies that assess patients referred from a clinical setting. Prevalence of any NPS in patients with Mild Cognitive Impairment (MCI) is from 35 to 85% (Monastero *et*

al., 2009). Interestingly enough, the prevalence of NPS has been reported to be as high as 27-29% in persons without cognitive decline, with depression (11.4%), aberrant night time behaviour (10.9%) and irritability (7.6%) being the most frequent symptoms (Geda *et al.*, 2008;Chan *et al.*, 2010). Geda and colleagues reported a significant difference in the prevalence of NPS in persons without cognitive decline and in patients with MCI. Apathy, agitation, anxiety, irritability and depression were all more prevalent in patients with MCI, having an OR above 2.5 compared to persons without any cognitive impairment (Geda *et al.*, 2008). The most prevalent NPS in patients with MCI were depression/dysphoria (27.0%), apathy (18.5%) and irritability/lability (19.4%). For patients with dementia, the prevalence of NPS in population based studies ranges from 61 to 88%, with apathy (27–57%) and depression (24-38%) being the most frequent (Lyketsos *et al.*, 2000;Ikeda *et al.*, 2004;Tatsch *et al.*, 2006).

2.2.5.2 Clinical out-patient studies

Several studies have used the NPI as an assessment scale for NPS, but nevertheless prevalence estimates in out-patients vary from 74% to 96%, indicating differences in the samples as well as in the dementia diagnosis (Steffens *et al.*, 2005;Benoit *et al.*, 1999;Petrovic *et al.*, 2007). One of the problems with prevalence studies in clinical settings is that some of the patients have been prescribed psychotropic medication, which may alter to what extent they express their symptoms. One study from Italy tried to avoid this problem, by including only patients with newly diagnosed AD who had not been prescribed any psychotropic medication. They reported a prevalence of 59.4% for at least one clinically significant NPS symptom (≥4 on a NPI sub item), with 38.2% of the patients having clinically significant apathy and 29.3% of the patients having an affective sub syndrome (NPI-depression + NPI-anxiety) (Spalletta *et al.*, 2010).

2.2.5.3 Long term care

Prevalence rates of NPS for patients in long term care settings have been presented in several studies in recent decades. Eighty-one percentage of patients in Norwegian nursing homes have dementia, and 72 % of the patients with dementia have a clinically significant NPS defined as at least one NPI item score ≥4 (Selbaek *et al.*, 2007). The most prevalent NPS in Norwegian nursing homes are irritability (present in 29.3% of the patients), apathy (29.1%) and aggression (26.6%). Zuidema estimated prevalence of NPS in 1,322 patients

in Dutch nursing homes, and measured with the NPH-NH they found that agitation/aggression, apathy and irritability were the most frequent symptoms (30–35%). Assessed by the CMAI, 85% of the patients had symptoms of agitation (Zuidema *et al.*, 2007). In 1990 Burns and colleagues published four studies describing the prevalence of NPS in 178 patients from nursing homes and outpatient clinics with AD, assessed by the Geriatric Mental State Schedule (GMSS) (Copeland *et al.*, 1976). They reported prevalence rates for delusion (10.7%), hallucination (11.3%), aggression (19.7%), wandering (18.5%) and apathy (40.5%) (Burns *et al.*, 1990d;Burns *et al.*, 1990c;Burns *et al.*, 1990b;Burns *et al.*, 1990a).

Prevalence rates can also be estimated from baseline data in longitudinal studies. Ballard *et al*. included 206 patients in a longitudinal study of NPS, 136 of them with a second assessment after one year (Ballard *et al.*, 2001a). Overall 76% of the patients had at least one clinically significant NPS (NPI ≥4) at baseline, 15% had delusions, 3% had hallucinations, 40% expressed aggression, 32% had aberrant motor behaviour and 18% had depression. Wancata *et al*. included 249 patients 60 years and older, and assessed them at baseline and after six months with the Clinical Interview Schedule (CIS) (Goldberg *et al.*, 1970). Thirty-eight percentages of the patients experienced some NPS at baseline, 30% had at least one depressive symptom while 12.7.5% had at least one symptom in the aggressive-psychotic syndrome (Wancata *et al.*, 2003). In a longitudinal study with 299 patients in long term care institutions from the Netherlands, the most prevalent NPS at baseline were irritability (28.2%), aberrant motor behaviour (23.1%) and agitation (20.5%) (Wetzels *et al.*, 2010b).

2.2.6 Course of the NPS

Several studies report the course of NPS, and they show heterogeneity in the course of the symptoms (Wetzels *et al.*, 2010a). Overall it has been estimated that up to 90% of patients with dementia will experience at least one NPS through the course of the disease (Robert *et al.*, 2005). The course of the NPS may be studied by categorising the patients with dementia according to dementia severity, or by following a cohort of patients with dementia with repeated assessments of NPS.

Prevalence of NPS according to the severity of the dementia

Most of the prevalence studies on NPS report an increased prevalence of NPS as the dementia becomes more severe. In a large study on NPS in Norwegian nursing homes, Selbæk *et al.* report an overall prevalence of NPS (any NPI item > 3) of 54.5% in mild dementia (CDR = 1), 69.7% in moderate dementia (CDR = 2) and 83.6% in severe dementia (CDR = 3) (Selbaek *et al.*, 2007). There was a statistically significant increase in the prevalence of delusions, hallucinations, aggression, apathy, disinhibition and aberrant motor behaviour as the dementia became more severe. In a study by Ballard *et al.* patients were assessed at baseline and after one year. At follow up the overall trend was that fewer patients expressed a clinically significant NPS, although hallucination (7%) and any NPS (82%) showed an increasing trend (Ballard *et al.*, 2001b).

Recurrence, persistence and resolution

Several studies have assessed NPS in a cohort of patients over the course of time, and so were able to record recurrence, persistence and resolution of NPS. "Persistence" is defined as the ratio of patients with Clinically Significant NPS (CS-NPS) at follow-up to patients with CS-NPS at the previous assessment, and "resolution" is the ratio of patients without CS-NPS at follow-up to the patients with CS-NPS at the previous assessment. "Recurrence" is the ratio of patients with symptoms at follow up to the patients with CS-NPS at one of the previous assessments. Studies on the course of NPS have been on both outpatients and those in long term care (Aalten *et al.*, 2005;Devanand *et al.*, 1997;Ballard *et al.*, 2001a;Wancata *et al.*, 2003;Wetzels *et al.*, 2010b;Selbaek *et al.*, 2008). Although the prevalence rate of symptoms remains stable, with only minor changes in the percentage of patients with NPS, the symptoms for each patient show an intermittent course. The studies report an overall high resolution rate of the NPS, with resolution rate from 57% to 87% (agitation sub-syndrome), from 56% to 75% (psychotic sub-syndrome), from 37% to 85% (depressive sub-syndrome) and 48% (apathy) (Wetzels *et al.*, 2010a). The fluctuation in resolution rate is caused by differences in the assessment tools, the time between assessments, the dementia diagnosis and the severity of the disease.

2.2.7 Possible causes and risk factors for NPS in dementia

The possible underlying causes for NPS in patients with dementia are many: biological and personal factors in the patient, alteration of neurotransmitters, genetic factors, brain

morphology and environmental factors, such as the attitudes and perhaps hostility in carers and relatives, and the physical environment of the patient's home or the institution in which they are living. The interactions between the causes are complex, and for an individual patient it is not possible to identify one single cause of NPS.

2.2.7.1 Neurochemical factors

Patients with dementia are found to have alterations in their neurotransmitter systems, due to increased or decreased levels of neurotransmitters, neuron loss or receptor loss, changes in the density of receptors, in the up-and-down regulation of receptors or a combination of the above mechanisms. Understanding the pathology of the neurotransmitter system in patients with dementia may direct the development of treatment options for NPS, as well as explaining the underlying causes of NPS.

Norepinephrine

Norepinephrine (NE) is a neurotransmitter both in the central nervous system (CNS) and in the peripheral nervous system. The NE concentration as well as the density of noradrenergic neurons are decreased in many areas of the brain in patients with AD, (Herrmann *et al.*, 2004). A correlation has been found between the severity of the AD and the level of NE dysfunction (Bondareff *et al.*, 1982), but the results are contradictory. Decreased function of the NE system is associated with such NPS as depression and anxiety, while increased levels of NE have been found in AD patients with aggression and agitation (Herrmann *et al.*, 2004). Loss of NE neurons in AD may lead to an acceleration of NE metabolism and hence an increase in NE activity (Hoogendijk *et al.*, 1999) .

Serotonin

Low levels of serotonin in the CNS are known to be associated with depression or anxiety in patients without dementia. This association is the basis for treating anxiety and depressive disorders with Selective Serotonin Reuptake Inhibitor (SSRI), which will increase the concentration of extracellular serotonin in the brain. The association between serotonin depletion and depression/anxiety is not as clear in patients with dementia. Studies with functional neuroimaging demonstrate serotonergic dysfunction both in patients with AD and FTD, but the location of the serotonergic dysfunction in the brain varies between studies (Salmon, 2007). In AD the numbers of 5HT2 receptors are often

decreased, which in studies have been associated with behavioural symptoms, but the effect of serotonin on cognition and depression in AD is less clear (Salmon, 2007). In FTD loss of serotonin receptors is found in the frontal and temporal cortex as well as in the nucleus raphe dorsalis. The serotonin dysfunction in FTD is linked with increased impulsivity and irritability, affective change, and changes in eating behaviour (Weder *et al.*, 2007).

Acetylcholine

Low levels of acetylcholine in patients with AD are associated with cognitive decline (Winkler *et al.*, 1998), which is the theoretical basis for the use of Acetylcholinesterase inhibitors (AchEI) in AD and DLB. Unfortunately, the effect of AchEI on cognition is limited (Clegg *et al.*, 2002). Acetylcholine has also been associated with NPS in patients with dementia. The limbic system and the nucleus basalis of Meynert are involved in the mediation of emotion, mood and motivation, and decreased levels of acetylcholine in these areas are found in AD and may be associated with NPS in patients with AD (Grossberg, 2005). Increased muscarinic M2 binding in the temporal and frontal cortex, inhibiting Ach–binding, were found to be associated with psychosis in a small sample of 26 patients with AD (Lai *et al.*, 2001), while decreased cholinergic function assessed post-mortem in brains of patients with AD were found to be associated with aggression (Garcia-Alloza *et al.*, 2005).

Gamma-aminobutyric acid (GABA) and Glutamate

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the human brain. GABA is present in the neocortex and the hippocampus, modulating the cholinergic and glutamatergic activity and thereby participating in the neuropathology of NPS, especially depression and apathy in AD (Limon *et al.*, 2011;Garcia-Alloza *et al.*, 2006). Glutamate is an excitatory neurotransmitter in the brain. In a small study (21 patients with AD) the regulation of glutamate was found to be affected in patients with dementia and a high anxiety score (Tsang *et al.*, 2008), but affection of the regulation of glutamate has not been demonstrated in patients with AD and depressive symptoms (Garcia-Alloza *et al.*, 2006). Although not demonstrated in clinical settings, there is a hypothetical possibility that a low concentration of glutamate in frontal and cingulated cortices correlates with agitation and irritability in dementia (Francis, 2009).

2.2.7.2 Genetic factors

Due to the strong familial aggregation of symptoms implicating genetic variation as a mediating factor in the development of those symptoms, many NPS studies in recent years have employed designs to study genetic association. Associations have been found between genetic factors and psychosis (Sweet *et al.*, 1998) and between genetic factors and agitation and depression (Tunstall *et al.*, 2000). Identification of genetic risk factors provides clinicians with the possibility of screening and targeting therapeutic strategies (Holmes *et al.*, 1998). Moreover, a few studies have reported preliminary findings positively associating a response to treatment with antipsychotics with polymorphisms already associated with the NPS themselves (Angelucci *et al.*, 2009;Dombrovski *et al.*, 2010), indicating a possible role for these polymorphisms in the cost effectiveness as well as the therapeutic effectiveness of treatment. A recent review shows that the results are contradictory (Michele-Sweet and Sweet, 2010). From a methodological perspective these differences are likely to be in part the result of four principal concerns: 1) small sample sizes; 2) differing definitions of syndromes; 3) differing criteria for a symptom to be recognised as ”clinically significant”; and 4) in those studies which use a cross-sectional method it is not always clear whether the phenotype under investigation will have had enough time to emerge as clinically significant.

Apolipoprotein E (ApoE) is a well established risk factor for AD. Persons with homozygotic ApoE ε4-allelles have an increased risk of developing AD compared to homozygotic ApoE ε3-allelles (OR=14.9) (Farrer *et al.*, 1997). Persons with heterozygote epsilon2/epsilon4 (OR=2.6) and epsilon3/epsilon4 (OR=3.2) also have an increased risk, while people with genotypes epsilon2/epsilon2 (OR=0.6) and epsilon2/epsilon3 (OR=0.6) have a decreased risk (Farrer *et al.*, 1997). Whether the ApoE ε4 polymorphism is related to NPS or not has been examined in several studies lately. Some studies indicating that ApoE ε4-allelles carriers are at risk of developing depression and apathy during the course of their AD, but other studies report no association between ApoE ε4 and depression in patients with dementia (Hirono and Cummings, 1999;Butters *et al.*, 2003;Cacabelos *et al.*, 1997). An association between AD, depression and ApoE ε4 was found in a recent study of 322 older patients, divided into three groups; patients with AD and NPS (N=93), patients with AD but without NPS (N=108), and patients with no cognitive impairment (No CI: N=121). Overall, they found no significant difference in the distribution of ApoE

genotypes between AD patients with and without NPS, but they reported that patients carrying ApoE ε4 had an increased risk of depression and apathy (D'Onofrio *et al.*, 2011). A Norwegian study found the same association, reporting that AD patients carrying an APOE ε4 allele were of higher risk of developing depression ($F = 4.14$; $p = 0.045$) than AD patients without an APOE ε4 allele (Fritze *et al.*, 2011).

Different receptor polymorphisms and transporter polymorphisms for serotonin and dopamine have been associated with NPS. One polymorphism of a serotonin transporter gene has been associated with psychosis in AD; one polymorphism of a dopamine transporter gene has been associated with agitation while a polymorphism in a dopamine receptor gene has been associated with mood symptoms in dementia (Proitsi *et al.*, 2010). Decreased density of serotonin transporters (SERT) is found in the prefrontal cortex of the brain in patients with AD, but no differences in transporter density was found between AD patients with and without severe depression (Thomas *et al.*, 2006). Polymorphisms of the dopamine receptors and transporter genes have also been associated with behavioural symptoms, such as sleep disturbance and aberrant motor behaviour (Proitsi *et al.*, 2010). The likelihood of depression is increased by five times in patients with AD and a polymorphism of the serotonin receptor genes (5HT2A and 5HT2C), compared to patients without a polymorphism (Holmes *et al.*, 2003). In a small study patients with DLB/PDD and depression had higher density of Serotonin 1A receptors in the temporal cortex than DLB/PDD patients without depression (Sharp *et al.*, 2008).

2.2.7.3 Structural and functional brain changes

The evolution of new technologies in brain imagining has allowed studies on the relationship between structural changes in the brain of patients with dementia and the NPS of the patients. Structural changes can be assessed with Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI), while functional changes in patients with dementia can be assessed with Single-Photon Emission Computed Tomography (SPECT), functional MRI (fMRI) and Positron Emission Tomography (PET). Nevertheless, the results in different studies are contradictory, probably caused by small sample size, heterogeneity in patients in terms of dementia diagnosis and severity, different assessment techniques and other methodological problems.

Cerebrovascular factors and depressive symptoms

Depression in dementia is associated with decreased blood flow in the prefrontal areas, the superior frontal and anterior cingular region, as demonstrated in two studies using PET technology (Hirono *et al.*, 1998;Holthoff *et al.*, 2005). Assessed by MRI, white matter hyperintensities in the frontal and right parietal lobe are strongly correlated with apathy and depression in Alzheimer's disease (Malloy *et al.*, 2007;O'Brien *et al.*, 1996;Starkstein *et al.*, 2009). Assessed by MRI, the same dysfunction in the fronto-subcortical circuits is found in patients with VaD and FTD with apathy (Malloy *et al.*, 2007). In a study of 116 persons with AD, VaD or DLB, the medial temporal lobe width on CT scanning was significantly greater in patients with depression than in patients with dementia, but there was no difference in width between patients with different dementia diagnoses (O'Brien *et al.*, 2000). Many articles report structural differences in the brains of patients expressing apathy and patients expressing depression. Assessed by MRI, structural brain dysfunction in patients with depressive symptoms and dementia is more located in the frontal deep white matter and basal ganglia, while patients with apathy have dysfunctions in the superior frontal and anterior cingular region (Malloy *et al.*, 2007). There are also convincing evidences for the association between cardiovascular risk factors early in life and depression later in life (Almeida *et al.*, 2007).

Functional brain changes

Functional dysfunction in the brain may be assessed by SPECT. Aggression in patients with dementia is in one study associated with decreased perfusion in the left anterior temporal lobe (Hirono *et al.*, 2000) and in another study associated with dysfunction in the right middle temporal lobe (Lanctot *et al.*, 2004), which makes the interpretation of the results difficult. The evidence is more convincing for FTD, where several studies assessing patients with SPECT have concluded that a dysfunction in the right frontal and temporal lobe is associated with aggression, antisocial behaviour or other socially undesirable behaviour (Mychack *et al.*, 2001).

Psychosis in dementia has been studied in patients with AD and DLB. Several studies have demonstrated, with the use of PET scans, dysfunction in the frontal, parietal, and temporal lobes in AD patients with psychosis, more specific hypoperfusion in the regions of the right parietal and left dorsolateral prefrontal cortex (Meeks *et al.*, 2006). Structural

imaging (CT) has also revealed an asymmetry in the frontal and temporal lobe in psychosis of AD (Geroldi *et al.*, 2002).

2.2.7.4 Environmental factors

Several environmental factors have to be considered as possibly contributing to the NPS of patients with dementia, but obviously there are methodological challenges when studying these factors. Much attention has been paid to the patient's physical environment in their home or in an institution. The development from nursing homes with large units to smaller Special Care Units (SCU) with fewer patients has been appraised by care givers and relatives, but research in the field is controversial. No DB RCT has been performed on the effect of SCU compared to ordinary nursing home units, but several non-RCTs comparing SCU with ordinary nursing home units have been published. Nevertheless, the results are difficult to interpret as only one study has examined the effect of SCU on one primary outcome (Bellelli *et al.*, 1998). Bellelli et al. report differences in symptoms seen in patients after admission to SCU. They reported a decrease in affective symptoms and agitation but no difference in psychotropic drug use after three months (Bellelli *et al.*, 1998). Overall, a favourable effect of SCU on affective symptoms, agitation, psychotropic drug use and use of physical restraints compared to ordinary nursing home units was reported in a recent Cochrane review, but no effect was found on the quality of life of the patients (Lai *et al.*, 2009).

The carers' influence on the patients and vice versa has been extensively studied, in an attempt to clarify the interaction between the carer and the patient. Professional carers obviously express different emotions towards the patients than relatives living with the patients do, but the interaction and emotions expressed between professional carers and the patients are important for the treatment of the patients. The Unmet Needs Model proposes that people with dementia are unable to articulate their needs and therefore react to adverse situations with behaviour that may be disturbing to others (Cohen-Mansfield, 2001).

2.2.7.5 Cognition

Cognition is connected to NPS, and the association is best understood as the prevalence of NPS increasing as the dementia becomes more severe (Selbaek *et al.*, 2007). As the cognitive function declines, in combination with loss of vision and hearing, the patients

with dementia will have problems interpreting input from the surroundings in which they live, which may lead to NPS. Loss of cognitive functions, such as motivation and executive functions, may also lead to inactivity, mimicking NPS such as apathy and depressive symptoms. In a cross-sectional study, examining 125 probably AD-patients with cognitive tests and NPI, García-Alberca *et al*. found that decline in cognitive function predicted NPS (Garcia-Alberca *et al.*, 2011). Although García-Alberca's study was small and is supported by few other studies, the finding is interesting and should encourage further research in the field.

2.2.7.6 Somatic diseases

NPS may be caused by, or worsened as a result of, somatic diseases. Hypothyroidism, for example, manifests itself with apathy, decreased energy, depressive symptoms and cognitive decline, which may be interpreted as NPS in dementia. Somatic diseases, such as urinary tract infections, constipation, anaemia or a broken bone may cause delirium in the patient. The clinical picture of delirium is fluctuating consciousness, hyper- or hypo activity, disturbances in day-night rhythm and disorganisation of behaviour, which may be difficult to differentiate from dementia with NPS. Delirium is more prevalent in patients with dementia than in patients without dementia, which could further complicate the separation of dementia with NPS from delirium. Pain in patients with dementia may be interpreted as a NPS. The verbal expression of pain is difficult for patients with moderate and severe dementia, and pain could manifest itself or be expressed as a NPS. In a RCT of 352 nursing home residents in western Norway, the group of patients receiving individual pain treatment had a significant reduction of agitation and other NPS compared to the group not receiving pain treatment (Husebo *et al.*, 2011). The strong association between cerebrovascular risk factors, stroke, dementia and depression later in life is discussed in chapter 2.2.7.6. NPS symptoms as apathy and depression is common after cerebrovascular incidents, and 30-50% of patients experience depressive symptoms post-stroke (Berg *et al.*, 2003;Hackett *et al.*, 2005).

2.2.8 Consequences of NPS

Neuropsychiatric symptoms are risk factors for the development of dementia. In a Chinese study with 321 patients, patients with Mild Cognitive Impairment (MCI) who showed NPS had an increased risk of progression to dementia compared to patients with MCI but

without NPS, most highly correlated in patients with depression accompanying the MCI (Chan *et al.*, 2011). Previous studies have also reported an increased risk of cognitive decline in patients with dementia and depressive symptoms (Wilson *et al.*, 2002). Other studies have reported that hallucination is a risk factor for progression to dementia caused by AD (Burns *et al.*, 1990b;Scarmeas *et al.*, 2005;Wilson *et al.*, 2000).

Different kinds of NPS have been associated with functional impairment. In a study of 523 patients with AD, anxiety was reported to be associated with ADL impairment (Teri *et al.*, 1999). Aggression was associated with functional impairment (Haupt *et al.*, 2000) in a study of 60 patients with AD, and in a study with 456 patients with AD followed for up to 14 years, psychosis was a risk factor for decline in both ADL function and cognition (Scarmeas *et al.*, 2005).

The concept of Quality of Life (QoL) in patients with dementia has been difficult to describe and therefore it has been difficult to agree upon a common definition of QoL in dementia. Several assessment scales have been developed to assess QoL in dementia. They have been used to study the association between NPS and QoL, but there is a discrepancy in the results. One study has reported an inverse association between NPS and QoL, increased prevalence of NPS being associated with a decreased QoL in a study of 101 patients with AD (Banerjee *et al.*, 2006), but other studies have shown no association between NPS and QoL (Ballard *et al.*, 2001c). In a systematic review of studies on the association between dementia and QoL, they found no association between decline in cognition or functional impairment and QoL, but they found an association between depression and lowered QoL (Banerjee *et al.*, 2009). A Norwegian study also reported an association between low QoL and severe depression (Barca *et al.*, 2011).

NPS cause distress for the carer and relatives of patients with dementia (Ulstein *et al.*, 2007;Black and Almeida, 2004). Several studies have studied the association between depression in carers of patients with dementia and NPS in the patient, but the results are contradictory (Black and Almeida, 2004;Donaldson *et al.*, 1997) showing a poor to moderate association. In patients with newly diagnosed PDD, relatives of the patients reported apathy, depression, anxiety and irritability caused most distress (Leiknes *et al.*, 2010).

Patients with dementia need nursing home placement earlier than persons without dementia (Luppa *et al.*, 2010), but also factors such as increased age of the patient or the carer, living alone and male gender contribute to institutionalisation. In patients with dementia cognitive impairment is associated with institutionalisation, but there is also an association between NPS and nursing home placement (Luppa *et al.*, 2008). Aggression had the highest hazard ratio for time to nursing home placement (HR 4.17), followed by hallucination (HR 2.54) and depression (HR 1.07) (Gilley *et al.*, 2004). NPS are also found to increase the cost of care for patients with dementia, estimated at an increased cost of $30 per month for each additional point on the NPI (Herrmann *et al.*, 2006).

2.2.9 Treatment

NPS cause distress for the patients and the carers, and much effort has been put into finding the best treatment for the different NPS. While research into pharmacological treatments for NPS dominated the field in the 1990s, the interest in research into non-pharmacological treatments for NPS increased in the following decade. The separation of treatment into pharmacological and non-pharmacological alternatives has been criticised, as the terms indicated that the non-pharmacological treatment is inferior to the pharmacological treatment (Cohen-Mansfield, 2001). It has been argued that the term non-pharmacological treatment should be replaced by the term psychosocial intervention. The term psychosocial intervention is unfortunately not perfect either, as some interventions are neither psychological nor founded on social theory, but the term psychosocial intervention will be used in this thesis.

2.2.9.1 Psychosocial interventions

Recently, reviews of the treatment of the NPS have stated that the treatment of choice for NPS is psychosocial intervention (Ballard and Corbett, 2010). As the gold standard for a double blinded randomised placebo controlled trial (DB RCT) is difficult to apply in studies of psychosocial interventions, most of the research into psychosocial intervention is by means of open trials or observational studies. The best evidence for the effect of psychosocial intervention in the treatment of NPS is for hand massage and touch therapy (Viggo *et al.*, 2006). Music therapy for patients with NPS may potentially reduce agitation in patients with dementia in the short term (Sung and Chang, 2005), although a Cochrane review using stricter criteria for the inclusion of studies in their meta-analysis concluded

that music therapy was of no effect for NPS (Vink *et al.*, 2004). Exercise is effective in increasing physical strength and balance, and the most consistent evidence in elderly patients with and without dementia showed that exercise increased sleep duration and decreased night-time awakenings (Heyn *et al.*, 2004). Conversely, a Cochrane review concluded that physical exercise was of no benefit in treating NPS for patients with dementia and NPS (Forbes *et al.*, 2008). For other psychosocial interventions, such as acupuncture, reminiscence therapy, validation therapy, aromatherapy, animal assisted therapy and light therapy, the evidence for its effect is poor (O'Neil *et al.*, 2011). The lack of evidence for psychosocial interventions might be caused by the study design, small study cohorts and methodological issues, but might also be caused by the lack of efficacy of the intervention. As well as intervening on the patient level, intervention on the staff level has been tried to improve the patients' NPS. Intervention may focus on the motivation of the staff, their knowledge of dementia as well as their attitude towards the patients. Several studies on staff education lack a control group, and their results should be treated with caution. Burgio *et al*. systematically trained nursing home staff in the treatment of NPS. Compared to a control group of nursing homes without specific behavioural management techniques, patients in the intervention nursing homes showed reduced agitation (Burgio *et al.*, 2002). It has also been demonstrated that learning non-verbal communication both reduced symptoms in patients and increased the well-being of the care givers (Magai *et al.*, 2002). Person-Centred Care (PCC) is a new way of thinking about dementia care, where the person with dementia is in focus, not the dementia disease. PCC was developed by Tom Kitwood and the relation to dementia is found in his book: "Dementia reconsidered: the person Comes First" (Kitwood T., 1997). Dementia-care mapping (DCM) is a method of implementing PCC in persons with dementia (Brooker, 2005). There are a couple of high quality studies on PCC. In a study from Australia, 324 patients with dementia from 15 sites were allocated to one of three treatment options: 1: DCM, 2: PCC; and 3: usually care (Chenoweth *et al.*, 2009). The analysis showed a statistically significant reduction in agitation and the use of antipsychotic drugs over time for patients receiving PCC and DCM compared to patients receiving the usual care. In another smaller RCT study of the effect of PCC used with patients in a bathing situation (a towel bath or usual care), the group of patients receiving the PCC or towel bath had significantly reduced agitation and aggression compared to that in the group of patients receiving the usual care (Sloane *et al.*, 2004). Other studies on PCC have been of poorer quality and the studies have had methodological limitations (Edvardsson *et al.*, 2008).

2.2.9.2 Pharmacological interventions

There has been extensive research on the effect of psychotropic drugs for NPS. Studies on the cause of NPS have revealed deficits in the neurotransmitter system of patients with dementia and NPS, which have been the theoretical basis for pharmacological interventions. Finding one psychotropic drug which is effective for all kinds of NPS is probably not possible, and clinicians should be encouraged to tie intervention to specific symptoms in their patients.

Antipsychotic medication

The experience with the effect of antipsychotic medication for psychosis in patients with Schizophrenia and other psychiatric diseases, induced optimism in treating psychosis in patients with dementia with antipsychotic medication. The effectiveness of antipsychotic medication for psychosis, agitation and aggression in dementia has been demonstrated in some studies (Brodaty *et al.*, 2003;Cummings *et al.*, 2002;De Deyn *et al.*, 2004), but the results are contradictory as other studies have reported no effect of antipsychotic medication for NPS (Schneider *et al.*, 2006). In reviews and meta-analyses the effect of atypical antipsychotic medication was demonstrated for risperidone (reducing aggression and psychosis) and aripiprazol (reducing aggression and psychosis), but the effect of the medication has to be balanced by the side effects of the medication (Ballard and Corbett, 2010). Studies on olanzapine and quetiapine did not indicate benefit of the treatment on NPS (Ballard and Corbett, 2010). Side effects in patients using antipsychotics are extra pyramidal side effects (EPS), decreased cognitive function, sedation and metabolic side effects. Newer atypical antipsychotics are believed to have fewer EPS than old typical antipsychotics, but atypical antipsychotics have been found to increase the risk of death and cerebrovascular disease in patients with dementia (Schneider *et al.*, 2005;Ballard *et al.*, 2011a). Cohort studies published thereafter indicated that typical antipsychotics might have even higher mortality rates than atypical antipsychotics (O'Brien, 2008;Gill *et al.*, 2005;Gill *et al.*, 2007). There are some indications of an association between agitation, aggression and psychosis in patients with dementia, which may have encouraged the use of antipsychotic medication for other NPS than psychosis in dementia (Rapoport *et al.*, 2001). Discontinuation studies of antipsychotic medication in patients with dementia and NPS have been beneficial to the patients (Bridges-Parlet *et al.*, 1997;Cohen-Mansfield *et*

al., 1999;van Reekum *et al.*, 2002;Ballard *et al.*, 2004;Ruths *et al.*, 2004;Ruths *et al.*, 2008;Ballard *et al.*, 2008;Ballard *et al.*, 2009).

Antidepressive medication

There are a few studies of the effect of antidepressants on NPS. Citalopram was reported to be effective in reducing all kinds of NPS in a study of 98 patients (Nyth and Gottfries, 1990). In a DB RCT study of 85 patients treated with citalopram, perphenazine or a placebo for up to 17 days, citalopram was found to be superior to a placebo in treating psychosis and behavioural symptoms (Pollock *et al.*, 2002). Nevertheless, four other studies reported that antidepressants were not more effective than a placebo for NPS (Auchus and Bissey-Black, 1997;Teri *et al.*, 2000;Lyketsos *et al.*, 2003;Finkel *et al.*, 2004), and a review concluded that antidepressants were not very effective in the treatment of NPS (Seitz *et al.*, 2011). Two studies have reported similar effects for citalopram as for risperidone in reducing agitation and psychosis in patients with dementia (Pollock *et al.*, 2007;Barak *et al.*, 2011). The side effects of antidepressants vary between the classes of antidepressants. Tricyclic antidepressants (TCA) are known to cause cognitive decline, sedation and cholinergic symptoms as dry mouth, while SSRI may cause symptoms from the gastro-intestinal tract (GI-tract). Traditionally, SSRI has been regarded as having fewer side effects than TCA, but a recent study reported that SSRI antidepressants have more severe side effects (death and cerebrovascular incidents) than classical TCA (Coupland *et al.*, 2011).

Cognitive enhancers

The effect of cognitive enhancers for NPS is controversial, as there are published studies with positive and negative effects (Ballard *et al.*, 2005;Finkel, 2004;Howard *et al.*, 2007). Best evidences are for the use of Acetylcholinesterase inhibitors (AchEI) for psychosis in patients with AD and DLB, as summarised in several meta-analysis and reviews (Grossberg, 2005;Sink *et al.*, 2005;Trinh *et al.*, 2003). Nevertheless, it has been commented that the small effect of AchEI on the treatment of NPS is of little clinical interest, although there is a statistically significant difference between the AchEI groups and the placebo groups (Sink *et al.*, 2005). The main side effects of AchEI are from the GI-tract, the AchEI are generally well tolerated in the elderly, and may therefore be the drug of choice in the treatment of psychosis in dementia. Memantine has been

demonstrated to be effective in treating symptoms of irritability/lability and agitation/aggression in patients with AD and NPS in patients with VaD (Ballard and Corbett, 2010). There are few studies on the effect of memantine for clinically significant agitation and aggression, and the evidence for the effect of memantine on psychosis is weak (Ballard and Corbett, 2010).

Antiepileptic drugs

With regard to antiepileptic drugs, the best evidence is for carbamezepine, with possible positive effect on agitation demonstrated in two small studies (Tariot *et al.*, 1998;Olin *et al.*, 2001). A Norwegian DB RCT with 103 patients found no differences in agitation or aggression between the oxcarbazepine and placebo group after 8 weeks treatment (Sommer *et al.*, 2009). The effect of other antiepileptic drugs has not been demonstrated (Ballard and Corbett, 2010).

2.3 Depression in the elderly

2.3.1 Depression in patients without dementia

The prevalence of depression increases with older age, see table 2 (Stordal *et al.*, 2001). Risk factors for depression in older age are solitude, somatic co-morbidity, previous episodes of depression, being female, experience of losses, having sleep disturbances, bereavement, functional impairments and low socio-economic status (Crown *et al.*, 2002;Cole and Dendukuri, 2003). Depression in old age is categorised as early-onset depression and late-onset depression, referring to whether the first episode of depression was before or after the age of 65 years. There is reason to believe that there is a substantial difference in early-onset and late-onset depression, in terms of epidemiology, pathology and the neurotransmitters involved in the disease, which should be taken into account when treating the depression, because later life depression is often linked to physical health (Alexopoulos *et al.*, 2002).

Table 2. Prevalence of depression in Norway, categorised according to age

Age	Men	Women
20-29 years	4.1 %	4.3 %
30-39 years	6.9 %	7.0 %
40-49 years	10.5 %	9.3 %
50-59 years	14.1 %	12.2 %
60-69 years	14.4 %	14.6 %
70-79 years	17.2 %	17.4 %
80-89 years	23.4 %	18.3 %

2.3.2 Depression in patients with dementia

Depressive symptoms, as part of the NPS syndrome, are found in up to 50 % of patients with dementia (Lyketsos and Olin, 2002). Even a depressive disorder, as defined in the DSM IV, ICD-10 or Provisional Criteria for Depression in Dementia, is frequent in patients with dementia as up to 20-25 % has the disorder (Lyketsos and Olin, 2002;Lyketsos *et al.*, 1997). The distinction between depressive symptoms of dementia, such as loss of interest and decreased initiative, and a depressive disorder is difficult for even an experienced geriatric psychiatrist to make. Depressive disorder in dementia is especially prevalent in patients with vascular dementia and in patients with Parkinson's disease. Up to 40% of patients with Parkinson's disease experience depression or depressive symptoms at least once during the course of their Parkinson's disease (Hanagasi and Emre, 2005). It has been suggested that depressive disorders in patients with dementia have a different clinical presentation than depressive disorders in patients without dementia, such as lack of interest and motivation, slowness of motor function and thoughts, and decreased response to pleasurable activities (Janzing *et al.*, 2002), but the hypothesis is contradictory as other studies have reported similarities in the depressive

symptoms in elderly patients with and without dementia (Engedal *et al.*, 2011;Starkstein *et al.*, 2005).

2.3.3 Assessment scales

Patients with dementia of moderate or severe degree may have problems in expressing their emotions, fear, and affections due to language problems and cognitive decline. The cognitive problems may even increase in patients with depression, which is problematic in the interpretation of their score on a depression rating scale based on interviews with the patients. Ordinary, well-known assessment scales for depression, such as the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), are therefore of limited use in patients with moderate or severe dementia. A couple of assessment scales have been designed for the elderly, including the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1982) and the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos *et al.*, 1988a). The GDS is not primarily developed for patients with dementia, and it fails to maintain validity in patients with mild to moderate dementia (Montorio and Izal, 1996). While the GDS is based on interviews with the patients, who have to respond with Yes/No answers, the CSDD is primarily based on observation by the carers. The CSDD is a questionnaire consisting of nineteen different items, each item is scored 0 (no symptoms), 1 (moderate symptoms) and 2 (severe symptoms). The CSDD has been translated into Norwegian, and is validated for patients living in Norwegian nursing homes (Barca *et al.*, 2010). According to the same study a cut-off point >8 for depression and a cut-off point >13 for severe depression are recommended (Barca *et al.*, 2010). Based on a factor analysis by Barca *et al*. the CSDD has been separated into a mood factor (sadness, anxiety, pessimism, suicidal thoughts, poor self esteem and delusion), a physical factor (appetite loss, weight loss, lack of energy and loss of interest), a cyclic factor (multiple night-time awakening, difficulty falling asleep and early morning awakening), a retardation factor (retardation and lack of joy) and behavioural factor (diurnal variation, irritability and agitation). One symptom, multiple physical complaints, did not load on any factor (Barca *et al.*, 2008). It is feasible to divide the factors into a mood sub-score and non-mood sub-score (Barca *et al.*, 2008). The original sub-scales suggested by Alexopoulos *et al*. contain different items, but these sub-scales were not based on a factor analysis (Alexopoulos *et al.*, 1988a). The CSDD is widely used both in clinical settings and in research, and has been found valid in patients

without dementia as well as in patients with dementia (Alexopoulos *et al.*, 1988b). The Hamilton rating scale for depression (HAM-D) (Hamilton, 1960) is not developed for the elderly or patients with dementia, but is still in use in the nursing home population. The HAM-D is a semi-structured 21-item questionnaire, with a cut-off point of 10/11 for depression. As the HAM-D is influenced by somatic symptoms and diseases, the use of HAM-D in the elderly population has been criticised. Nevertheless the HAM-D demonstrated its validity in a study of patients with terminal cancer (Olden *et al.*, 2009).

2.3.4 Treatment of depression

The treatment options for patients with depression and coexisting dementia are the same as for patients without dementia; psychosocial treatment, Electroconvulsive Treatment (ECT) and antidepressant medication. While the evidence for psychosocial treatment for depression in elderly patients without dementia is strong (Cuijpers *et al.*, 2006), the evidence for psychosocial treatment for depression in dementia is weak (Verkaik R *et al.*, 2005). However, one review has suggested that psychosocial treatment for depression is effective even in patients with dementia (Wilkins *et al.*, 2009). Electroconvulsive therapy (ECT) is often used as the last treatment option for depression when treatment with antidepressant medication has failed or been proven ineffective. Most of the evidence for ECT in elderly patients with depression is from patients without cognitive impairment, but one small study of patients with depression comparing patients with no cognitive impairment, MCI and dementia, demonstrated that ECT was equally effective in all three groups of patients (Hausner *et al.*, 2011). All three patient groups had transient cognitive decline after the ECT treatment, but even the patients with dementia regained pre-ECT cognition scores 6 months after the final treatment with ECT.

Antidepressants are frequently prescribed to patients with dementia. Almost 40 percentage of patients in Norwegian nursing homes are prescribed antidepressants on a regular basis (Selbaek *et al.*, 2007). The indication for the use of antidepressants is sometimes unclear or poorly documented. The evidence for the use of antidepressants for depression in patients with dementia is weak. Several DB RCTs have studied the effect of antidepressants on depression in patients with dementia, and they are all summarised in table 3. Most of the studies are against medication, but the results diverge. This inconsistency in the results and conclusions are caused by the heterogeneity of the studies, in terms of number of included patients, type and severity of the dementia, the severity of

Table 3. Randomised controlled trials of antidepressants on depression in patients with dementia

Study	No of participants	Study drug	
1. Reifler et al 1989	*n*=28	imipramine	= placebo
2. Nyth et al 1992 and 1994	*n*=98/29	citalopram	> placebo
3. Roth et al 1996,	*n*=694	moclobemid	> placebo
4. Petracca et al 1996	*n*=21	clomipramine	> placebo
5. Magai et al 2000	*n*=31	sertraline	= placebo
6. Petracca et al, 2001	*n*=41	fluoxetine	= placebo
7. Lyketsos et al 2003	*n*=44	sertraline	> placebo
8. V. Cunha et al 2007	*n*=31	venlafaxine	= placebo
9. Rosenberg et al 2010	*n*=133	sertraline	= placebo
10. Weintraub et al 2010	*n*=133	sertraline	= placebo
11. Banerjee et al 2011	*n*=326	mirtazapine	= placebo
		sertraline	= placebo

the depression, the type and dosage of the medication, the assessment methods and the duration of the study period. The lack of evidence of the effect of antidepressants for depression in dementia is confirmed in meta-analysis. The conclusions of two meta-analyses are against the use of antidepressants (Bains *et al.*, 2002;Nelson and Devanand, 2011), while one meta-analysis concludes that antidepressants are more effective than a placebo (OR = 2,32, CI 1,04 - 5,16 and NNT = 5 for response and OR = 2,75, CI 1,13 – 6,65 and NNT = 5 for remission) (Thompson *et al.*, 2007). The selection of studies in Thompson's meta-analysis is, however, slightly different from the other two meta-analyses, explaining the discrepancy in the conclusion. The three latest published DB

RCTs on the effect of antidepressants for depression in patients with dementia are of good quality and cover a large number of patients. All three studies are against the use of sertraline compared to a placebo, and one study is against the use of mirtazapine compared to a placebo as well (Rosenberg *et al.*, 2010;Weintraub *et al.*, 2010;Banerjee *et al.*, 2011). At the moment there is no evidence that the use of antidepressants is superior to a placebo in the treatment of depression in patients with dementia.

3. Previous studies related to the four papers of this thesis

3.1 The validation of the Norwegian version of the Severe Impairment Battery

In recent decades several cognitive tests for patients with dementia have been developed and are in clinical use. Some of them are used for screening for cognitive dysfunction, such as the Mini Mental State Examination, while other cognitive tests have been developed to assess more specific cognitive functions, such as the Trail Making Test A and B (Folstein *et al.*, 1975;Reitan RM, 1955), comprehensively described in chapter 2.1.2.

Most of the cognitive tests for patients with dementia are developed for patients with mild to moderate dementia. When testing patients with severe dementia the psychometric properties of the tests do not allow observation of changes in cognitive function over time, nor will they be able to separate differences in cognitive function in different patients. This so-called floor effect of cognitive tests inspired a research group at the McGill Centre for Studies on Aging, St Mary's Hospital, Montreal, to develop a new cognitive test especially for patients with moderate to severe dementia (Panisset *et al.*, 1994). The original Severe Impairment Battery (SIB) is a 57-item questionnaire, minimum score zero and maximum score 133, which can be divided into nine cognitive domains: social interaction, memory, orientation, language, attention, praxis, visuospatial and constructional abilities, and orientation to name. The SIB was later revised into a 51-item questionnaire (minimum score zero, maximum score 100) (Schmitt *et al.*, 1997). The SIB takes 20-30 minutes to complete, which is the maximum attention span for patients with severe dementia. Therefore, a short version of the SIB, the SIB-S, was developed with help of exploratory factor analysis (EFA) and consensus meetings, reducing the original SIB to a 26-question version (minimum score zero, maximum score 52 (Saxton *et al.*, 2005). An even shorter version of the SIB, the SIB-8, with eight questions (minimum score zero, maximum score 16) was developed by analysing four DB RCT that had been using the 100 points version of the SIB to evaluate changes in cognitive function after treatment with cognitive enhancers (Schmitt *et al.*, 2009). The eight questions were chosen by analysing sensitivity to change and ease of administration. The SIB and its short versions have been translated into and validated in several different languages (Suh and

Kang, 2006;Ahn *et al.*, 2006;Hugonot-Diener *et al.*, 2003;Pippi *et al.*, 1999;Llinas *et al.*, 1995;de Jonghe *et al.*, 2009).

3.2 Course of the NPS in nursing homes

There are several studies on the course of NPS in patients with dementia in nursing homes, comprehensively reviewed by Wetzels *et al*. (Wetzels *et al.*, 2010a). They identified 18 studies on the course of NPS in nursing homes. The same year, Wetzels and colleagues published a study on the course of NPS over a two year period in Dutch nursing homes (Wetzels *et al.*, 2010b). Of the nineteen studies identified, only seven studies were primarily designed to study the course of NPS in patients with dementia (Burton *et al.*, 1995;Wagner *et al.*, 1995;Ballard *et al.*, 2001a;Payne *et al.*, 2002;Wancata *et al.*, 2003;Selbaek *et al.*, 2008;Wetzels *et al.*, 2010b), and only four of them studied a broad range of NPS (Ballard *et al.*, 2001a;Wancata *et al.*, 2003;Selbaek *et al.*, 2008;Wetzels *et al.*, 2010b).

The seven studies on the course of NPS in patients in nursing homes differed in terms of number of patients included, assessment scales, time interval between assessments and time from first to last assessment (table 4). Burton *et al*. described a sample of 201 patients in a longitudinal cohort study. Of the 201 patients, 79 patients received antipsychotics and 122 did not receive antipsychotics. The patients were assessed with the Psychogeriatric Dependency Rating Scale (PGDRS), an assessment-scale describing nine different disruptive behaviours, at baseline and after one year (Burton *et al.*, 1995). Their main conclusion was that in patients prescribed antipsychotics disruptive behaviour was more prevalent, more persistent and had a higher incidence rate than in patients not prescribed antipsychotics. While persistence of disruptive behaviour in patients not prescribed antipsychotics was 4-5% after one year, the persistence of disruptive behaviour in patients prescribed antipsychotics was 13-14%. In the study by Wagner *et al*. 298 patients with dementia (mostly AD) were assessed three times over a period of four months with the Memory Behaviour Problems Checklist-NH (MBPC-NH) (Wagner *et al.*, 1995). The MBPC-NH is a 24-item assessment tool evaluating behaviour in patients with dementia (Teri *et al.*, 1992). The main conclusion in the paper by Wagner *et al*. was that the patients were as likely to experience an occurrence of a new behaviour problem as a drop in behaviour problems between baseline and four months.

Table 4. Studies on the course of the NPS in nursing homes

Author (Year)	N	Follow up	No of assessments	Assessment Instrument	Residence
Wetzels et al., 2010	117	2 yrs	5	NPI-NH	SCU
Selbaek et al., 2008	633	1 yr	2	NPI-NH	NH
Wancata et al., 2003	86	6 months	2	CIS	NH
Payne et al., 2002	201	1 year	3	CSDD	NH
Ballard et al., 2001	136	1 year	2	NPI-10	3 SCU/3 NH
Wagner et al., 1995	298	4 months	3	MBPCNH	SCU
Burton et al., 1995	201	1 year	2	PGDRS	NH

N = No of patients, NPI-NH = Neuropsychiatric Inventory – Nursing Home edition, SCU = Special Care Unit, NH = Nursing Home, CIS = Clinical Interview Schedule, CSDD = Cornell Scale of Depression in Dementia, NPI-10 = Neuropsychiatric Inventory 10 items edition, MBPC-NH = Memory Behaviour Problems Checklist-NH, PGDRS = Psychogeriatric Dependency Rating Scale

Ballard *et al*. assessed 136 patients in three special care units (SCU) and three nursing home wards with the NPI-10 assessment scale twice over a period of 12 months (Ballard *et al.*, 2001a). They reported a persistence rate of 41-43% for agitation symptoms, 25% for hallucination, 43% for delusion and 32% for depression. Payne *et al*. followed a group of 201 patients with depressive symptoms (CSDD>12) with three assessments over one year, and found a persistence rate for depression of 15% (Payne *et al.*, 2002). Wancata *et al*. assessed a group of 86 patients with the Clinical Interview Schedule (CIS) at baseline and

after 6 months (Wancata *et al.*, 2003). The CIS is a semi-structured interview developed to study psychiatric morbidity (Goldberg *et al.*, 1970). After six months the persistence rate for depressive symptoms and aggressive-psychotic symptoms were 63.3% and 73.1%, respectively. Selbæk *et al*. included 933 patients with dementia, where 633 patients completed the follow-up assessment after one year (Selbaek *et al.*, 2008). The patients were assessed with the NPI-NH twice over one year, and persistence rates were calculated; 52.9% for agitation/aggression, 58.0% for irritability, 42.1% for hallucinations, 44.1% for delusions, 44.5% for anxiety and 52.2% for depression. Finally, in the study by Wetzels *et al*. 117 patients were assessed twice a year for two years with the NPI-NH. The persistence rate for the different NPI items were: agitation/aggression (52.9–62.4%), disinhibition (9.6–33.6%), irritability (37.6–56.1%), aberrant motor behaviour (41.9–62.8%), hallucination (50%), delusion (13.2–36.2%), depression (17.6–39.5%), apathy (36.0–54.8%), euphoria (17.6–39.5%) night time behaviour (0-56.7%) and eating abnormalities (14.2–50.0%) (Wetzels *et al.*, 2010b).

Overall, the studies on the course of NPS in nursing homes differ in their results, but the trend is that while the patients' persistence rate of at least one NPS is high between assessments, the individual NPS fluctuate in their nature and show an intermittent course (Wetzels *et al.*, 2010a).

3.3 Discontinuation of antidepressants and NPS

Previously, no DB RCT on the discontinuation of antidepressive medication in patients with dementia has been published. The only randomised and controlled antidepressant discontinuation study in elderly patients was by Ulfvarson *et al*., who in a single blind RCT studied discontinuation of antidepressive medication (SSRI) in 70 patients with no dementia or history of depression, and with no anxiety or a major depressive disorder (Ulfvarson J *et al.*, 2003). Half of the patients were randomised to discontinuation, and there were no differences between the two groups, either at three or at six months in terms of depressive symptoms as measured with MADRS, a global assessment of functioning and side effects.

3.4 Discontinuation of antipsychotic medication and NPS

Antipsychotic medications are used for NPS in dementia. In a study by Selbæk *et al*. 24% patients in Norwegian nursing homes were prescribed antipsychotic medication (Selbaek *et al.*, 2007). The Norwegian Medical Agency (NMA) recommends discontinuing antipsychotics after three months' prescription when used for NPS. Antipsychotics do have serious adverse effects, such as cerebrovascular incidents, dizziness, sedation, decreased cognitive function and Parkinsonism (Felleskatalogen, 2011). In 2004 the NMA warned against prescription of risperidone and olanzepine for elderly patients with dementia as published data showed a three-fold increase in cerebrovascular incidents in patients prescribed risperidone and olanzepine (Schneider *et al.*, 2005;Brodaty *et al.*, 2003). Later, a similar increased risk of cerebrovascular incidence has been demonstrated in typical antipsychotics as in atypical antipsychotics (Gill *et al.*, 2005;Gill *et al.*, 2007). Multi medication is a problem in geriatric patients, and we know that geriatric patients are vulnerable to adverse effects and interactions.

Several studies have reported that the discontinuation of the treatment of antipsychotic medication in patients with dementia and NPS is safe and has even been beneficial for the patients (Bridges-Parlet *et al.*, 1997;Cohen-Mansfield *et al.*, 1999;van Reekum *et al.*, 2002;Ballard *et al.*, 2004;Ruths *et al.*, 2004;Ballard *et al.*, 2008;Ballard *et al.*, 2009;Ruths *et al.*, 2008).

4 The thesis

4.1 Objectives

The overall objective of the project was to study the neuropsychiatric symptoms (NPS) of patients with dementia in nursing homes, the course of the symptoms and the effect of the withdrawal of antidepressive medication. To be able to evaluate changes in cognitive function over time in patients with moderate and severe dementia, the Severe Impairment Battery (SIB) was translated into Norwegian.

The main objectives in this thesis were:

- To investigate the validity and reliability of the Norwegian version of the SIB
- To describe the prevalence and distribution of NPS in patients with dementia in Norwegian nursing homes
- To explore the course of the NPS in patients with dementia in Norwegian nursing homes
- To study the effect of the discontinuation of antidepressive medication in patients with dementia and NPS in Norwegian nursing homes

4.2 The subjects

The four aims of the thesis were examined in four sub studies including different subjects and the results are reported in four articles.

4.2.1 Severe Impairment Battery validation study

In the validation and reliability study of the SIB 59 patients from three nursing homes in the counties of Hedmark and Oppland were recruited. A non-randomised group of nursing home patients were invited to take part in the study, and based on the Clinical Dementia Rating Scale (CDR) score, the patients were categorised into mild, moderate and severe dementia groups. We ensured that equal numbers of patients with mild, moderate and severe dementia were recruited. The patients or their relatives gave their written consent before inclusion in the study.

4.2.2 The course of NPS in Norwegian nursing homes

All of the patients in seven nursing homes in Hedmark and Oppland were invited to take part in the study on the course of NPS in patients with dementia. Of the 271 patients screened for inclusion 61 patients were not included. Twenty-nine patients declined participation, twenty-five relatives declined on behalf of the patients, two patients moved out of the nursing home before data collection commenced, one patient had a terminal illness, and four patients were not asked to participate because the nursing home staff deemed it improper to ask for the consent. Of the 210 patients included in the study, 169 patients were suffering from dementia, defined as a score of one or more on the CDR (Hughes *et al.*, 1982).

4.2.3 The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes – an open pilot study

In the small pilot study on the discontinuation of antidepressive or antipsychotic medication, patients were recruited from seven nursing homes in Hedmark and Oppland. The nursing home doctors screened for eligible patients in the nursing homes or in selected wards of the nursing homes, and contacted the patients or relatives to obtain written consent. Forty-one patients were screened for inclusion, 18 patients failed the screening procedure (14 patients declined participation; four patients did not fulfil the inclusion criteria). Of the 23 patients recruited, 11 patients were using antidepressive medication and 12 patients were using antipsychotic medication at inclusion. All the included patients in the study discontinued the prescribed antidepressive or antipsychotic medication.

4.2.4 Discontinuation of antidepressants in patients suffering from dementia and NPS in Norwegian nursing homes – the DESEP study

To ensure representativeness of the cohort, patients in the DESEP study were recruited from 52 nursing homes in 14 counties in Norway. The recruitment of patients was done by 16 study centres, and they were either a department of geriatric psychiatry or a large nursing home with a special interest in dementia. Two-hundred-and-five patients were assessed for eligibility, 77 patients were excluded for the following reasons: not meeting the inclusion criteria (n=25), declined to participate (n=29), depressive disorders (n=19),

other psychiatric disease (n=1) and other reasons (n=3). Patients or relatives gave their written consent before the patients were included in the study.

4.3 Methods

4.3.1 Data collection

For all four studies, the assessment of the patients was done in a similar way, although the questionnaires used were slightly different. Registered nurses underwent a one-day standardised training course to ensure a common way of applying the questionnaire. The patients' cognitive function was assessed by an interview with the patients with a standardised cognitive test, the Severe Impairment Battery (SIB) (Saxton and Swihart, 1989). The patients' quality of life was assessed by the Quality of Life – Alzheimer Disease (QoL-AD) (Logsdon and Albert, 1999), a questionnaire either answered by the patient, the carer or both. The degree of dementia, extra pyramidal side-effects (EPS) and the level of function were assessed with the CDR (Hughes *et al.*, 1982), the Unified Parkinson Disease Rating Scale (UPDRS, six-item version) (Ballard *et al.*, 1997), and the Lawton & Brody's Physical Self-Maintenance scale (PSMS) (Lawton and Brody, 1969), respectively. NPS were assessed by the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) and depressive symptoms were assessed by the Cornell Scale of Depression in Dementia (CSDD) (Alexopoulos *et al.*, 1988a).

The Neuropsychiatric Inventory (NPI)

The NPI has been described in detail in chapter 2.2.3, and the study nurses filled in the questionnaire about the patient based in information from the carers in the nursing homes. In the two discontinuation studies we used the 10-item version of the NPI (NPI-10), while in the study on the course of the NPI we used the 12-item version (NPI-12). A clinically significant NPS (CS-NPS) was defined as a score >3 on an individual subscore.

The Cornell Scale of Depression in Dementia (CSDD)

The CSDD has previously been described in chapter 2.3.3, and was filled in based on information from the carers in the nursing homes. In the DESEP study we used the factor analysis from Barca *et al*. to divide the CSDD score into a mood-score and a non-mood score (Barca *et al.*, 2008).

The Severe Impairment Battery (SIB)

The SIB has been discussed in chapters 2.1.2 and 3.1. In the small pilot discontinuation study and the DESEP study we used the 100-point version of the SIB, and the cognitive test was given to the patients.

The Clinical Dementia Rating Scale (CDR)

The CDR is described in chapter 2.1.2, and was administrated to the carers in the nursing homes, and filled in based on observations of the patients. The total CDR score was obtained by using the scoring rules given by the Washington University CDR-assignment algorithm (Morris, 1993).

The Quality of Life – Alzheimer Disease (QoL-AD)

The QoL-AD is a 13-item questionnaire designed to obtain a rating of the patient's Quality of Life from both the patient and the carer (Logsdon *et al.*, 1999). The language in the questionnaire is straightforward, and the assessment scale is developed for patients with dementia (feasible for patients with MMSE scores of 10 or higher) (Logsdon *et al.*, 1999). Carers completed the measure as a questionnaire, while patients were interviewed about their own QoL. During the interview the patients had a written text with the four possible answers in front of them, and were given the opportunity to point out their answers. The measure consists of 13 items, rated on a four-point scale, with 1 being poor and 4 being excellent (minimum total score 13, maximum score 52).

The Unified Parkinson Disease Rating Scale (UPDRS, six-item version)

The UPDRS is developed to assess the symptoms in patients with Parkinson's disease, and is used to evaluate their response to treatment and the course of the symptoms over time. The UPDRS consists of five parts, evaluating mental symptoms, motor symptoms, ADL and other symptoms. Ballard *et al*. isolated six items from the UPDRS that could be used to evaluate Parkinsonism in patients with DLB, but could also be used to evaluate Extra Pyramidal Symptoms (EPS) in patients using antipsychotics (Ballard *et al.*, 1997). Each item is scored on a 5-point scale from 0 (normal) to 4 (severe symptom), and the six items are added up to a maximum of 24 points. Ballard *et al*. reported a specificity of 100% and a sensitivity of 85% for significant Parkinsonism in DLB using a cut-off of 7/8 points on the UPDRS 6-item version.

The Lawton & Brody's Physical Self-Maintenance scale (PSMS)

Lawton and Brody's scale for the assessment of ADL was developed for use among elderly persons living at home or in institutions. It comes in a self-reporting and an observational version; in our studies we used the observational version. The scale is based on the theory that activities can be arranged hierarchically, where some activities are more complex than others. The PSMS measures physical ADL function, in contrast to Instrumental ADL (IADL). The scale consists of 6 items. A 5-point scale for responses ranges from total independence (1 point) to total dependence (5 points). The total score ranges from six to 30; a higher score indicates greater impairment.

4.3.2 The Severe Impairment Battery validation study

The aim of the study was to determine the validity and reliability of the Norwegian version of the Severe Impairment Battery (SIB). The SIB was developed by J. Saxton and colleagues to measure cognitive function in people with moderate to severe dementia (Saxton and Swihart, 1989). The SIB had not previously been translated into Norwegian, and therefore had not been validated and tested for reliability. Three psychiatrists translated the English version of the SIB to Norwegian. A fourth psychiatrist made a final Norwegian version by compiling the three Norwegian versions into one. A British-born colleague who had been living in Norway for several decades translated the final Norwegian version back into English, and the re-translated version was virtually identical to the original English version.

The study consisted of two parts, a validation study and an inter-rater reliability study. In the inter-rater reliability study 30 patients were included. Inclusion criteria were dementia of mild, moderate or severe degree, assessed by the CDR, and having given written consent. The patients were tested with the SIB twice, by a physician and a registered nurse, 1-7 days apart. In the validation study the same 30 patients were included, but the cohort was extended with an additional 29 patients. All 59 patients were tested with the SIB as well as the CDR, and the correlation between the SIB score and the CDR was calculated.

4.3.3 The course of NPS in Norwegian nursing homes

In the study 210 patients were included, where 169 patients had dementia defined as a CDR score > 0.5. The inclusion criteria were that the patient was living in the nursing home and had given written consent. All patients included in the study were assessed by the NPI, the CDR, the CSDD and the PSMS at baseline and every fourth month for 16 months, totalling five assessments. In the paper we report the course of the NPS as assessed by the NPI, where a clinically significant NPS (CS-NPS) was defined as a NPI score>3 on an individual item. We calculated point prevalence at each assessment, cumulative prevalence over 16 months, incidence between two assessments (four months) and cumulative incidence for the whole study period (16 months). We also assessed persistence and resolution. Persistence is the ratio of residents with CS-NPS at follow up to residents with CS-NPS at the previous assessment, and resolution is the ratio of residents without CS-NPS at follow up to the residents with CS-NPS at the previous assessment.

4.3.4 The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes – an open pilot study

The study was an open study with two groups of eleven and twelve patients. Patients were recruited from nursing homes in Oppland and Hedmark. In group 1 the patients discontinued antipsychotics; in group 2 the patients discontinued antidepressants. The antidepressive or antipsychotic medication was tapered out over one week. On the basis of previous studies, the drop-out rate was estimated to be 30%. All the patients included in the study were recruited from nursing homes, and were believed to be living under similar conditions as regards quality of care, environment and medical follow-up during the study period of 24 weeks. Patients were examined by standardised assessment tools at baseline, and after 3 weeks, 6 weeks, 12 weeks and 24 weeks. The project leader made a follow-up telephone call to the nursing homes two weeks after the study drug was discontinued, concerning patient safety and adverse symptoms. Throughout the entire study period the project leader was in contact with the staff of the nursing homes to ensure the well-being of the patients. To ensure a correct dementia diagnosis, all current patients had a review of clinical data and medical history before entering the study. The inclusion and exclusion criteria were:

Inclusion Criteria*:*

1) Dementia in Alzheimer's disease and / or vascular dementia.
2) Clinical Dementia Rating (CDR) 1, 2 or 3
3) Nursing home resident for three months or more
4) Group 1: Regular prescription of antipsychotics of any kind for three months or more
5) Group 2: Regular prescription of antidepressants of the SSRI type for three months or more

Exclusion Criteria*:*

1) Other dementia disease
2) Schizophrenia, depression or other psychiatric diagnosis
3) Expected survival less than 3 months
4) Acute infection 10 days before inclusion
5) Uncontrolled Diabetes Mellitus (DM)
6) Terminal illness
7) Group 1: Antipsychotic medications used to control nausea

Data collection

All the interviews with the patients and the carers, and all the rest of the data collection, were done by the project leader. The patients were interviewed and assessed for cognitive function and quality of life by means of the SIB and the QoL-AD. The rest of the assessment tools were administered by means of interviews with the registered nurse or health care worker most familiar with the patient. At baseline and after 24 weeks the patients were examined with the SIB, the NPI, the CSDD, the CDR, the UPDRS six-item version, and the PSMS. At three, six and twelve weeks the patients were assessed with the NPI and the UPDRS. At baseline demographic data and information on psychotropic drug use were gathered from the medical records and the carers.

4.3.5 Discontinuation of antidepressants in patients suffering from dementia and NPS in Norwegian nursing homes – the DESEP study

Organisation of the project

One project leader (MD) and one project coordinator (registered nurse) held full-time positions at the Centre for Old Age Psychiatry Research, Innlandet Hospital Trust. Sixteen study centres in 14 counties in Norway cooperated with the project leader and the project coordinator to select patients. Every study centre provided one principle investigator (a geriatric psychiatrist or general practitioner trained in geriatric psychiatry) and one to three research nurses. The study centres were either old age psychiatry departments at hospital trusts or nursing homes with a special interest in geriatric psychiatry. Each study centre recruited patients from nearby nursing homes. Patients were recruited from 52 nursing homes.

Study design

The DESEP study was a 25-week, double-blind parallel group, randomised placebo controlled discontinuation trial of four SSRIs; escitalopram, citalopram, sertraline and paroxetine. Participants were nursing home residents (men and women).

The inclusion criteria were:

1) Patients with a diagnosis of dementia in Alzheimer Disease (AD), Vascular Dementia (VaD) or mixed AD/VaD (as defined in the International Classification of Diseases, version 10, diagnostic criteria for research)
2) Clinical Dementia Rating 1, 2 or 3.
3) Nursing home residents for more than four weeks
4) Regular prescription of risperidone, escitalopram, citalopram, paroxetine or sertraline for the last three months.

The exclusion criteria were:

1) Dementia of any other origin
2) A clinical history of a depressive disorder or schizophrenia
3) Severe somatic disease or terminal illness
4) Not being able to take tablets/capsules as prescribed
5) Expected survival less than three months.
6) Poorly controlled Diabetes Mellitus.
7) Acute infections within the past 10 days

No changes in the dose of the current antidepressant medication were allowed in the last four weeks before inclusion and throughout the study period. Changes in the prescription of psychotropic drugs other than antidepressants during the study period were allowed.

The first week after baseline assessment, the antidepressants were either tapered off and replaced by a placebo (antidepressant discontinuation group, ADG) or replaced by a study drug containing active medication (same kind and same dose) as before inclusion (antidepressant continuation group, ACG).

Randomisation and masking

The patients were randomised by a computer generated randomisation process (1:1) in blocks of four. The randomisation lists were prepared at the Department of Statistics, Oslo University Hospital. Name and date of birth for included patients were sent to the Hospital Pharmacy, Innlandet Hospital Trust, and the packs of study medication were prepared there according to the randomisation lists. The randomisation was kept hidden from the participants, the carers and the assessors until the completion of the data collection and the statistical analyses had been done. Randomisation was done across study centres and nursing homes.

Assessments and outcomes

The project leader and the project coordinator trained all the research nurses about the study protocol and the questionnaires in a one-day training course. A geriatric psychiatrist or general practitioner trained in geriatric psychiatry studied the participants' medical records and if necessary examined the patient, to ensure correct diagnosis of dementia and to ensure exclusion of patients with a depressive disorder. The research nurses collected

all the data from the nursing homes, closely supervised by the project leader and the project coordinator to ensure reliable data collection.

Assessments were done at baseline, and at day 28 (+/- 2 days), 49 (+/- 3 days), 91 (+/- 5 days) and 175 (+/- 7 days). Table 5 shows which assessments instruments that were administrated at the various assessment times.

Table 5. Overview over assessments instruments that were administrated at the various assessment times

Assessment scale	Baseline	Day 28	Day 49	Day 91	Day 175
Neuropsychiatric Inventory	X	X	X	X	X
Clinical Dementia Rating	X				X
Severe Impairment Battery	X				X
Quality of Life – Alzheimer Disease	X				X
Cornell's Scale of Depression in Dementia	X	X	X	X	X
Lawton & Brody's PSMS	X				X
Unified Parkinson's Disease Rating Scale	X	X	X	X	X

PSMS = Physical Self-Maintenance Scale

Efficacy assessments were made at baseline, and at four, seven, 13 and 25 weeks. Primary endpoints were changes in the CSDD and the NPI after 25 weeks. The CSDD (minimum score zero, maximum score thirty-eight) assesses the depressive symptoms of the patients with dementia. In Norway a score of eight points and above is regarded as a sign of a depressive disorder, while a score of thirteen and above is regarded as a sign of a severe

depressive disorder (Barca *et al.*, 2010). The CSDD was divided into two sub-scales, mood (sadness, anxiety, pessimism, suicidal thoughts, poor self-esteem and delusion) and non-mood (the remaining 13 symptoms); according to a recent Norwegian factor analysis (Barca *et al.*, 2008). The NPI 10-item version assesses the NPS, and includes the sub-items; delusions, hallucinations, agitation/aggression, depression, anxiety, apathy, irritability, euphoria, disinhibition and aberrant motor behaviour. The frequency scores are multiplied by the severity scores. If the resulting score is equal to or greater than 4, the symptom is regarded as clinically relevant. If the score is equal to or greater than 9, the symptom is regarded as severe (Steinberg *et al.*, 2004). The NPI was divided into the following sub-syndromes: Affective (NPI-depression and NPI-anxiety), Psychosis (NPI-hallucinations and NPI-delusions), Agitation (NPI-agitation, NPI-irritability and NPI-disinhibition) and Apathy (NPI-apathy) (Selbaek and Engedal, 2011).

The secondary endpoints were changes after twenty-five weeks on the UPDRS, QoL-AD, the PSMS, the SIB and the CDR. The SIB was used on the patients unless they were unable to communicate or refused testing. The QoL-AD was given to both the patients and the carers. The additional assessments were given to one of the nurses at the nursing home.

4.4 Statistics

The data was analysed using the Statistical Program for Social Science (SPSS) vs 15.0, and the significant p-value is 0.05.

4.4.1 The Severe Impairment Battery validation study

To test for differences between the patients' characteristics we used the t-test for independent groups and the chi-square test. The Cronbach's alpha was calculated to evaluate internal consistency of SIB. The Spearman's correlation coefficient between the SIB and the CDR was calculated. We used the Spearman's rho test to analyse inter-rater reliability for the total SIB score and all the sub-scores, and the Mann–Whitney U-test to assess differences in the total SIB scores for different stages of CDR. Finally, a Receiver Operating Characteristic (ROC) curve was used to calculate sensitivity, specificity and accuracy, and a Likelihood Ratio for a positive test (LR+) and for a negative test (LR-) for the SIB score. The likelihood ratio is an estimate of how much a test result will change the odds of having a disease, in our example the association between a cut-off value of the

SIB and CDR groups. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1- specificity), while the likelihood ratio of a negative test result (LR-) is (1-sensitivity) divided by specificity. The ROC curve was used to calculate the probability of correctly labelling the severity of the dementia and to find the cut-off values between different CDR groups.

4.4.2 The course of NPS in Norwegian nursing homes

First, we did an exploratory analysis, and the differences between patients with complete and incomplete data were analysed with an independent student's t-test and Chi-square test for continuous and categorical data, respectively. Non-parametric statistics were used for data that was not normally distributed. We calculated point prevalence, cumulative prevalence, incidence, cumulative incidence, and persistence and resolution rates for each of the 12 items of the NPI. Point prevalence is the proportions of patients with a CS-NPS at each assessment, and cumulative prevalence is the proportions of patients with a CS-NPS on at least one of the five assessments. Incidence is the proportion of patients who were symptom free at one assessment, but developed a CS-NPS at the next assessment. Cumulative incidence is the proportion of patients who were symptom free at baseline but developed a CS-NPS at one of the following assessments. Persistence is the ratio of residents with CS-NPS at follow up to residents with CS-NPS at the previous assessment, and resolution is the ratio of residents without CS-NPS at follow up to the residents with CS-NPS at the previous assessment. To analyse the variation in severity of the NPI-score over time, we used the linear multiple level model (MLM). MLM is a good statistical technique for analysing hierarchically organised data with repeated assessments, and also for use when data are missing (Field, 2009).

4.4.3 The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes – an open pilot study

We did an exploratory analysis, and the baseline characteristics were analysed with the independent Student's t-test for parametric data, the Mann–Whitney U-test for non-parametric data and chi-square statistics or Fischer's exact test for categorical data. Differences between baseline and 24 weeks were analysed with the Student's t-test for parametric data, the Mann–Whitney U-test for non-parametric data and chi-square statistics or Fischer's exact test for categorical data.

4.4.4 The discontinuation of antidepressants in patients with dementia and NPS in Norwegian nursing homes – the DESEP study

The power calculation was based on the only published pilot study on the discontinuation of antidepressants in persons with dementia (Bergh and Engedal, 2008). Based on a statistical power of 80%, a two-tailed significance level of 0.05 and a drop-out rate of 33%, 45 patients had to be included in each group to ensure enough statistical power to detect a 30% change in the CSDD score. The corresponding numbers were 76 patients in each group to detect a 30% change in the NPI score. We had planned to enrol 152 patients in the study, but the inclusion rate was slow, and only 128 patients were included.

All 128 patients were included in the safety analysis, and all the patients with at least one assessment after the baseline (117 patients) were included in the efficacy analysis. The last-observation-carried-forward method (LOCF) was used to impute values if follow-up data were missing. We also analysed the patients with complete data (n=81) for changes in the primary endpoints, presented as observed cases. Assessment scales which lacked more than 20% of the data were not analysed. Analyses were done across study centres without sub-analyses of each study centre, as ten study centres were small (they had less than ten patients each).

The baseline characteristics were analysed with the independent Student's t-test for parametric data, Mann–Whitney U-test for non-parametric data and chi-square statistics or Fischer's exact test for categorical data. The two study groups were compared with an independent Student's t-test for the difference between baseline and 25 weeks for the two primary outcomes; CSDD and NPI. Differences between the two groups after 25 weeks were analysed with the Student's t-test for parametric data, the Mann–Whitney U-test for non-parametric data and chi-square statistics or Fischer's exact-test for categorical data. For the primary outcomes Analysis of Covariance with correction for baseline data of the CSDD and the NPI was done. A post hoc test comparing the two study groups' changes in the CSDD and the NPI at visit 2, 3 and 4 was done.

4.5 Ethics

In all research that makes use of patients there are ethical dilemmas that have to be considered and discussed. The pros and cons of the study for each individual patient, the group of patients and the society should be discussed. The disadvantages for the patients

enrolled in the study should be avoided or kept at a minimum compared to the benefits for the patients. Treatment and intervention studies should be compared with the results of the best treatments known at the time of the trial. A placebo controlled trial should not be carried out if there is a good tried and tested treatment for a disease. The persons included in the study should give written, informed and voluntary consent to participate. Many patients with dementia have limited insight into their illness and have a limited capacity to understand the information relating to a study. In Norwegian nursing homes 80.5% of the patients have dementia, and 26.7% have moderate and 33.6% have severe dementia (Selbaek *et al.*, 2007). A considerable proportion of these patients will have a reduced ability to give informed consent because they lack the capacity. In our studies, carried out among nursing home patients, the staff together with the consultants assessed whether a patient had the capacity to give informed consent or not. Patients who could give informed consent gave written consent. If not, we informed the next of kin, and the next of kin could refuse participation in the studies on behalf of the patient.

As we wanted to study the course of the NPS as well as the effect of the withdrawal of antidepressants on NPS in patients with dementia, all our studies included patients with dementia. Our studies could not, therefore, be carried out among patients without dementia. Failing to do studies among patients with dementia because they cannot give consent would be unethical because the patients would miss the opportunity of receiving evidence based treatment. For the SIB validation study and the study on the course of NPS in nursing homes, the patients were assessed with standardised questionnaires which contributed to the patients' having a better medical investigation than they usually would have had. There were no disadvantages for the patients in taking part in the study apart from the collection of potentially sensitive data and the time the patients were occupied with the interviews, and we judged that the benefit of being in the studies exceeded the disadvantages.

For the two drug discontinuation studies special ethical considerations had to be taken into account. Usually withdrawals of well-established treatments are questionable, especially if the evidence for their effects is well documented. We wanted to study the effect of the discontinuation of drug treatment for NPS in patients with dementia. According to evidence-based reviews, such as Cochrane reviews, the effects of antidepressant and antipsychotic medication for NPS are not well documented. Besides, treatments with such

drugs are reported to have serious adverse effects and interactions with other drugs make drug treatment complicated in the elderly. Without having solid evidence for significant effects of psychotropic drugs on patients with dementia, it may be unethical to prescribe antidepressants and antipsychotics for elderly patients with dementia. Based on previous discontinuation studies and our pilot study, our hypothesis was that the patient's symptoms would be unchanged or improve after discontinuation of antidepressants.

The studies were approved by the Norwegian Medicines Agency, the Regional Committee of Medical Research Ethics and the Norwegian Directorate of Health. They were conducted according to the standard of Good Clinical Practice (GCP), and the DESEP was monitored by independent persons from Oslo University Hospital. The procedures were conducted in accordance with the Helsinki Declaration as revised in 1983.

5 Abstracts of the papers with additional results

Paper I

Reliability and validity of the Norwegian version of the Severe Impairment Battery (SIB)

Objective: The Severe Impairment Battery (SIB) is developed to test cognitive function in patients with dementia of moderate to severe degree. We have conducted a study to assess the inter-rater reliability and the validity of the Norwegian version of SIB.

Methods: The reliability study comprised 30 patients, and the validity study 59 patients in nursing homes. We assessed Cronbach's alpha coefficient of the scale and the inter-rater reliability for the total SIB score and its nine sub scores between two testers by means of the Spearman's correlation coefficients. In the validity study we compared the SIB scores with the scores on the Clinical Dementia Rating Scale.

Results: The mean SIB score was 72.10 (SD 25.37). The Cronbach's alpha was 0.97, and the inter-rater reliability of total SIB score was Spearman's rho 0.85, and ranged from 0.46 to 0.76 for the nine sub-scores. The mean SIB score for patients with a CDR score<2 was 84.2(13.4), whereas total scores for patients with CDR 2 and 3 were 74 (18.9) and 48.4 (33.3), respectively. A cut-off point of 80.5 points gave the highest accuracy in discriminating between patients with CDR 2 and CDR 3, while a cut-off point of 87.5 best discriminated between CDR<2 and CDR 3.

Conclusion: The study indicates that the Norwegian version of SIB is a reliable and valid test with which to evaluate the cognition in patients with dementia of moderate to severe degree.

Paper II

The course of neuropsychiatric symptoms in patients with dementia in Norwegian nursing homes

Background: Neuropsychiatric symptoms (NPS) are common in patients with dementia, and cause distress for patients. Studies on the prevalence, incidence, persistence and resolution of NPS in patients living in nursing homes are sparse. The aim of this study was to evaluate the course of NPS in patients with dementia living in Norwegian nursing homes.

Methods: 169 patients from seven Norwegian nursing homes were assessed five times over a period of 16 months with the Neuropsychiatric Inventory (NPI). The severity and the frequency of the NPI were analyzed.

Results: 91.7% of the patients had at least one clinically significant NPS at one or more assessments over the 16 months. Irritability (63.5%), agitation (51.0%) and disinhibition (50.0%) had the highest cumulative prevalence, while irritability (42.6%), disinhibition (37.8%) and depression (31.5%) showed the highest cumulative incidence. Delusion, agitation and irritability were enduring symptoms while the other symptoms had high resolution rates. The severity of the NPS did not vary significantly over time.

Conclusion: Almost every patient in Norwegian nursing homes had at least one clinically significant NPS over 16 months, but individual NPS show a fluctuating course. This should influence how we monitor and treat NPS in patients with dementia.

Paper III

The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes – an open pilot study

Introduction: The prevalence of dementia in Norwegian nursing homes (NH) is 80%, 72% of those have Behavioural and Psychological Symptoms of Dementia (BPSD), and 25.8% were prescribed antipsychotics and 39.0% antidepressants. Five double blind randomised trials (DB RCT) have evaluated the effects of the withdrawal of antipsychotics from patients with BPSD. None of these studies report changes in the patients' symptoms after withdrawal. No DB RCT has studied withdrawal of antidepressants in patients with BPSD. The aim of the open pilot study was to examine BPSD and depression after withdrawal of antipsychotic or antidepressant medication in patients with dementia and BPSD.

Methods: We conducted a 24-week open antidepressant and antipsychotic withdrawal study with 23 patients. Medication was tapered out over 1 week. Patients were examined at baseline and after 24 weeks by means of the Neuropsychiatry Inventory (NPI), Severe Impairment Battery (SIB), Quality of Life–Alzheimer Disease (QoL-AD), Cornell's Depression Scale (CSDD), Lawton's PADL, the Unified Parkinson Disease Rating Scale (UPDRS) and the Clinical Dementia Rating Scale (CDR). In addition, assessment of the NPI and the UPDRS were done at weeks 3, 6 and 12.

Results: Mean age was 84.1 (SD 6.59) years, and 91.3% were women. Three patients were rated as CDR 1, 11 as CDR 2 and nine as CDR 3. Ten patients completed 24 weeks, six in the AP and four in the AD group. The NPI scores increased slightly in both groups after discontinuation of medication, but showed minor changes at the end of the study period. The CSDD were unchanged in the antipsychotic group, but decreased in the antidepressant withdrawal group. This trend was confirmed when analysing the sub items depression and anxiety of the NPI.

Conclusion: Although our findings are not statistically significant and the number of patients is small, the present study does show a trend towards decreased depressive and BPSD symptoms after the withdrawal of antidepressants. We plan to carry out a DB RCT of the withdrawal of antidepressants.

Paper IV

A double blind, randomized placebo controlled discontinuation trial of antidepressants in persons with dementia and neuropsychiatric symptoms – the DESEP study

Background: Forty percent of nursing home residents in Norway are prescribed antidepressants, but with unclear indications. Twenty percent of patients with dementia have clinically significant depressive symptoms. The evidence for the efficacy of antidepressants for Neuropsychiatric Symptoms (NPS) is weak.

Methods: A twenty-five week double-blind antidepressant discontinuation RCT was performed, on nursing-home residents with dementia and NPS, without a depressive disorder (According to ICD-10 criteria). The primary outcomes were changes on the Cornell Scale of Depression in Dementia (CSDD) and the 10-items version of the Neuropsychiatric Inventory (NPI) after 25 weeks, while secondary outcomes were changes on the Clinical Dementia Rating Scale, the Unified Parkinson Disease Rating Scale, the Quality of Life – Alzheimer Disease, the Lawton & Brody's Physical Self-Maintenance scale and the Severe Impairment Battery.

Findings: There was a significantly different mean change between baseline and 25 weeks between the two groups in the CSDD score, 2·53 (SD 5·61, worsening) in the antidepressant discontinuation group (ADG) and minus 0·43 (SD 3·61, improving) in the antidepressant continuation group (ACG), p=0·001. The mean total score for the NPI-10 increased by 5·93 (SD 19·41, worsening) in the ADG and decreased by 1·39 (SD 15·26) in the ACG, p=0·023. A non-response analysis (>30% worsening on the CSDD) confirmed these results, as significantly more patients in the ADG (22·0%) worsened compared to the ACG (10·3%), p=0·006. No statistically significant differences between the groups were found for secondary outcomes.

Interpretation: Patients in the ADG experienced more depressive symptoms assessed by the Cornell Scale of Depression in Dementia and more NPS assessed with the Neuropsychiatric Inventory.

Funding: The study was funded by unrestricted grants from the Innlandet Hospital Trust, the Research Council of Norway and the South-Eastern Norway Regional Health

Authority. H. Lundbeck A/S provided the study with escitalopram tablets and placebos free of charge.

Additional results: A post-hoc analysis, with the independent student's T-test, of the changes in the mean total CSDD score from baseline to assessment 2 (four weeks), assessment 3 (seven weeks) and assessment 4 (thirteen weeks) showed the following.

Visit 2: ADG = +0.39 (SD 3.86), ACG = -0.77 (SD 3.28), p=0.097

Visit 3: ADG = +1.61 (SD 5.39), ACG = -0.88 (SD 3.15), p=0.003

Visit 4: ADG = +2.33 (SD 5.69), ACG = -0.21 (SD 4.46), p=0.009

6 Discussion

The overall objective of the project was to study the neuropsychiatric symptoms (NPS) of patients with dementia in nursing homes, the course of the symptoms and the effect of withdrawal of antidepressive medication. To be able to evaluate changes in cognitive function over time in patients with moderate and severe dementia, the Severe Impairment Battery (SIB) was translated into Norwegian. This thesis is based on the research project and its four articles. A discussion of the four main objectives of the project is to be found in chapter 6.1 to chapter 6.5.

6.1 The validity and reliability of the Norwegian version of the SIB

The Norwegian version of the SIB was translated from the English version in traditional ways with a translation and then a re-translation back into English. We report a high Cronbach's alpha, in agreement with previous studies, indicating a good internal consistency of the cognitive test. Furthermore, we report the inter-rater reliability with a Spearman correlation coefficient of 0.85 (p-value<0.001) for the total SIB score, while the Spearman correlation coefficient for the SIB subscales ranged from 0.46 to 0.76. This indicates a lower inter-rater reliability in our study for the Norwegian versions of the SIB compared to versions in other languages, as other studies report a Spearman correlation coefficient of 0.97 to 0.99 for the inter-rater reliability (Panisset *et al.*, 1994;Suh and Kang, 2006;Llinas *et al.*, 1995;Pippi *et al.*, 1999;Ahn *et al.*, 2006). These five studies reporting a higher correlation all used a different methodology to study the inter-rater reliability than that which we used. In our study the project leader and a registered nurse tested the patients on different days, at least one day apart and maximum seven days apart. In the other five studies one rater tested the patients while another rater was present at the same interview and scored the SIB simultaneously. The difference in methodology may explain the differences in the Spearman correlation coefficients between the studies, as our test procedure was a mix of an inter-rater and a test-retest reliability study. The other studies report a test-retest reliability correlation coefficient between 0.81 and 0.97, which corresponds with our inter-rater reliability correlation coefficient. There were also differences in the severity of the dementia and dementia diagnosis of the patients between the studies, which could explain the differences in the correlation coefficients. We included patients with mild, moderate and severe dementia independent of the aetiological dementia diagnosis. Suh *et al*. and Ahn *et al*. included patients with moderate and severe

AD (Suh and Kang, 2006;Ahn *et al.*, 2006) and Panisset *et al*. included patients with AD with a mean Mini Mental State Examination (MMSE) score of 10.7 (Panisset *et al.*, 1994). In the study by Pippi *et al*. patients with different kinds of dementia disorders were included, and they reported the weakest inter-rater test correlation coefficient of the five studies (Pippi *et al.*, 1999).

In the validation study we compared the SIB score with the CDR score, and reported a Spearman correlation coefficient of -0.55, indicating a lower score on the SIB as the CDR score increased. Suh *et al*. reported a Spearman correlation coefficient of -0.67 comparing the SIB score and the CDR score, which was slightly higher than in our study. The difference is probably explained by the fact that the Korean population was more homogeneous than ours. The other four studies compared the SIB score with the MMSE score, reporting a Spearman correlation coefficient between 0.73 and 0.87.

We reported a statistically significant difference in the SIB score between the patients with CDR 1, CDR 2 and CDR 3, indicating that the SIB could discriminate between the three severities of dementia. Using a Receiver Operating Characteristic (ROC) curve analysis and a cut-off point of 80/81 we could discriminate between patients with CDR 2 and CDR 3 very well, and using a cut-off point of 87/88 we could discriminate between patients with CDR < 2 and CDR 2. Ahn *et al*. reported a cut-off point of 62/63 to discriminate between patients with CDR 2 and CDR 3, indicating that patients in the Korean study with moderate and severe dementia on average performed less well on the SIB compared to the Norwegian patients. The differences in the cut-off point may be explained by differences in the translation and the implementation of the Korean and the Norwegian versions of the SIB and the CDR. Another explanation could be differences in the interpretation of the CDR scale between researchers in the two countries, as there is some room for subjectivity when scoring the assessment scale.

Other cognitive tests, such as the MMSE, have a floor effect when used in patients with moderate and severe dementia. A floor effect of a test exists if more than 15% of the respondents achieved the minimum score of the test (McHorney and Tarlov, 1995), and therefore the tests are not useful in testing cognitive function in patients with severe dementia. The SIB has been used for evaluating the effect of donepezil treatment on cognition in patients with dementia in several large RCT (Winblad *et al.*, 2006;Feldman *et*

al., 2001), and has been found to be able to detect changes in cognitive function over time in a group of patients.

The Norwegian version of the SIB is valid and reliable and may be used for patients with moderate and severe dementia. We conclude that the SIB is useful in evaluating the effect of treatment on the cognitive function of patients, as well as in assessing the course of cognitive function in the patients.

6.2 The prevalence and distribution of NPS in patients with dementia in Norwegian nursing homes

In our study we report the prevalence, incidence, persistence and resolution of NPS in patients with dementia in Norwegian nursing homes. Prevalence may be reported as point prevalence, at inclusion or at a later time of assessment, or as a cumulative prevalence defined as the presence of a symptom at one or more assessments during the study period. Point prevalence may vary between studies because of differences in assessment instruments or study population. Cumulative prevalence may differ between studies because of the time period studied and the frequency of assessments, as well as differences in assessment instruments and the study population. Comparisons of our results with other studies are difficult because of substantial differences in methodology, use of assessment instruments, the severity of the dementia and dementia diagnosis in the patients studied. We report that irritability (35.1%), agitation (32.3%) and disinhibition (25.9%) were the most prevalent NPS in Norwegian nursing homes, assessed as point prevalence at baseline. These findings correspond well with other studies (Ballard *et al.*, 2001a;Selbaek *et al.*, 2007;Zuidema *et al.*, 2007;Wetzels *et al.*, 2010b). The similarity in the prevalence of NPS in nursing homes in different countries could indicate that the prevalence of NPS is correlated with the dementia disease rather than environmental factors or differences between the nursing homes studied.

Wetzels *et al*. reported similar cumulative prevalence for most of the NPI sub-items over a 24 month study period as we did over a 16 month study period, but for four of the sub-items (delusion, hallucination, depression and disinhibition) the cumulative prevalence in the Dutch study was 50% lower than the cumulative prevalence in our study (Wetzels *et al.*, 2010b). The patients in the study by Wetzels *et al*. had more severe degree of dementia than those in our study. The mean MMSE score was 7.6 (SD 7.1) in the Dutch

study vs. a mean MMSE score of 14.5 (SD 6.0) in our study. More severe dementia is usually associated with a higher prevalence of NPS (Selbaek *et al.*, 2007), but in the Dutch study both the point prevalence and the cumulative prevalence of delusion, hallucination, depression and disinhibition were lower than in our study. Both studies included patients with dementia, independent of aetiological dementia diagnosis, the patients lived in nursing homes, age and gender were comparable between the studies and both studies used the NPI for assessment of the symptoms. What could the reasons be for the differences?

One explanation could be differences in the analysis of the data from patients where questions in the questionnaire were answered with the "not applicable" (N/A) – option. In our study, data from patients where questions were answered “not applicable” were excluded from the prevalence analysis; while in the Dutch study symptoms that could not be evaluated (due to the patients’ language or communication problems) were scored as zero and the data were included in the prevalence analysis (Wetzels, personal communication). As answering questions about the presence of delusion or hallucinations may be difficult for patients with dementia, evaluating these symptoms may be unreliable. Scoring symptoms impossible to evaluate as zero will reduce the prevalence rate of the symptoms in that cohort of patients.

Another explanation for the difference in the occurrence of depressive symptoms between the two studies could be differences in the prescription of psychotropic medication. However, this is probably less likely, since the patients in our study used antidepressants and anxiolytics drugs more frequently than patients in the Dutch study. Conversely, patients in the Dutch study were more frequently prescribed antipsychotic drugs than patients in the Norwegian study, which could explain the lower prevalence of psychosis and disinhibition in the study by Wetzels *et al*. (Wetzels *et al.*, 2010b). In another Dutch study, by Zuidema *et al*., the prevalence rates of the NPS are comparable to the prevalence rates we report, except for delusion and hallucination which have lower prevalence figures in the Dutch study than in our study (Zuidema *et al.*, 2007). Our study and the study by Zuidema et al. were comparable in terms of the mean age of participants, male/female distribution, types of nursing homes and assessment instruments used in the study. The Dutch study scored symptoms that were impossible to evaluate as zero, in the same way as the study by Wetzels, which could explain the differences between Zuidema et al.’s study

and ours. The differences in the frequency of psychotic symptoms could also be explained by the more frequent use of antipsychotic medication in Dutch nursing homes (Zuidema *et al.*, 2007).

The present study has yielded improved knowledge of prevalence rates of NPS in Norwegian nursing homes. This knowledge can prepare the municipalities (which are responsible for nursing-home care in Norway) in their planning for the health care system of the future. Our study population was from seven nursing homes in two counties of south-eastern Norway, and the nursing homes were chosen for reasons of convenience and not by random selection. We should, therefore, be careful when generalizing the results of our study to all the patients living in nursing homes in Norway. However, the prevalence rates of the NPS in our study were directly comparable with the prevalence rates in another large Norwegian nursing-home study, which included a representative sample of 1,163 patients from 26 nursing homes in 18 municipalities and four counties. This might indicate that the other results in our study are reliable as well.

6.3 The course of NPS in patients with dementia in Norwegian nursing homes

Comparison of studies on the course of NPS in nursing homes is perhaps even more difficult than the comparison of studies on the prevalence of NPS. There are huge differences in the number of assessments and the time between assessments, among studies on the course of NPS in patients with dementia living in nursing homes. In addition, differences in the severity and aetiology of the dementia in the patients, differences in the assessment instruments used in the study, different cut-off points used to classify a NPS as a clinically significant symptom, and different prescription rates of psychotropic drugs in the nursing homes make comparison of studies difficult. The seven studies on the course of NPS in nursing homes are summarized in table 4 in chapter 3.2, and, as can be seen there, the studies vary in terms of assessment instruments, time between assessments and the number of assessments (Wagner *et al.*, 1995;Burton *et al.*, 1995;Ballard *et al.*, 2001a;Payne *et al.*, 2002;Wancata *et al.*, 2003;Selbaek *et al.*, 2008;Wetzels *et al.*, 2010b). The studies of Ballard *et al*., Selbæk *et al*. and Wetzels *et al*. are, however, the studies most comparable to our study, as they included patients with various dementia disorders living in nursing homes. The patients had similar demographic data as in our study, and they were assessed with the NPI.

In our study delusions, agitation/aggression, depression, disinhibition, irritability and aberrant motor behaviour showed the highest persistence rates over the five assessments, corresponding with the results of other studies (Wetzels *et al.*, 2010b;Ballard *et al.*, 2001a;Selbaek *et al.*, 2008). Wetzels *et al*. reported that agitation/aggression, disinhibition and irritability were the most persistent NPS (Wetzels *et al.*, 2010b), Selbæk *et al*. reported that irritability, agitation/aggression and apathy were the most persistent NPS (Selbaek *et al.*, 2008), while Ballard *et al*. reported that the persistence rate of agitation/aggression and delusions were higher than the persistence rate of hallucinations and depression (Ballard *et al.*, 2001a).

In our study, appetite and eating disorder, sleep and night-time behaviour disorder and euphoria had the highest resolution rate, which did not correspond to the findings of the other studies. Ballard *et al*. reported that hallucinations and depression had high resolution rates (Ballard *et al.*, 2001a), Selbæk *et al*. found that euphoria, aberrant motor behaviour and hallucinations had highest resolution rates (Selbaek *et al.*, 2008) and Wetzels *et al*. reported that delusions, disinhibition and euphoria had the highest resolution rates (Wetzels *et al.*, 2010b). Explanation for this variation in resolution rates could be due to the dropout rates during the study period, the differences in time between assessments, the number of assessments during the study period and the differences in the use of psychotropic drugs. Several studies indicate, however, that the NPS fluctuate over time irrespective of psychotropic drug use, and the correlation between the frequency of NPS and the use of psychotropic drugs is low (Selbaek *et al.*, 2008;Ballard *et al.*, 2001a). Caution should be taken in the interpretation of the association between the prevalence and the course of the NPS and the psychotropic drug, as the studies referred to are observational studies.

We reported no statistically significant differences in the severity of NPS during the follow-up period. Other studies have found a decrease in the severity of symptoms with increasing severity of the dementia (Wetzels *et al.*, 2010b;Selbaek *et al.*, 2008). Explanations for the different results could be (1) increased awareness of the patients' NPS among the nursing-home staff, which caused the staff to report higher prevalence and severity of the NPS during the study period, (2) the study period in our study was too short to demonstrate changes in the severity of the symptoms, (3) patients with severe dementia died during the study period, which caused a stable distribution of the NPI score for the

study population; and (4) the increased severity of dementia is associated with the increased use of psychotropic drugs, which could camouflage the symptoms.

We conclude that individual NPS fluctuate over time and this fluctuation should have clinical implications for the treatment of patients with dementia. Psychotropic drug use should be monitored closely in patients with dementia and the drugs should be discontinued if the NPS are not present any more.

6.4 The effect of discontinuation of antidepressive medication in patients with dementia and NPS in Norwegian nursing homes

We have published a small open pilot study on the discontinuation of antidepressant and antipsychotic medication in patients with dementia and NPS. As the study was open, with no control group, the results of the study should be interpreted with caution. The biggest lesson learned from the pilot study was that it was feasible to withdraw psychotropic drugs, as this was safe for the patients. Further, we learned that the assessment instruments used in the study were reliable and valid for the design chosen. We report trends from our study indicating no changes in the NPS after discontinuation of antipsychotic medication, which were in line with previous antipsychotic discontinuation studies (Bridges-Parlet *et al.*, 1997;Cohen-Mansfield *et al.*, 1999;van Reekum *et al.*, 2002;Ballard *et al.*, 2004;Ruths *et al.*, 2004;Ruths *et al.*, 2008;Ballard *et al.*, 2008;Ballard *et al.*, 2009). In the group of patients whose antidepressants were discontinued, we found a 50% reduction in the depressive symptoms assessed with the Cornell Scale of Depression in Dementia (CSDD), which raises some questions. Was the higher prevalence and severity of depressive symptoms at inclusion an expression of the adverse effects of the antidepressant prescribed? Did the carers in the nursing homes report a decrease in depressive symptoms after 25 weeks, because our hypothesis was that nursing-home patients in Norway were over-medicated? Anyway, the results encouraged us to conduct a double blind randomized controlled trial (DB RCT) on the discontinuation of antidepressants.

As far as we know, we have conducted the first double blind RCT discontinuation study of antidepressant medication on patients with dementia and NPS living in nursing homes, meaning that our results have to be discussed in the light of the results in clinical trials on the initiation of antidepressant drug therapy rather than discontinuation studies. Ulfvarson *et al*. have published a single blind antidepressant discontinuation study of patients

without dementia and with no known depressive disorder (Ulfvarson J *et al.*, 2003). The clinicians treating the patients were aware of the discontinuation of antidepressants in half of the patients, but the raters were blinded to whether or not an individual patient had discontinued treatment. They found no differences between the discontinuation group and the continuation group.

In our DB RCT discontinuation study we found an increase in depressive symptoms in the group of patients discontinuing their antidepressant medication. Several DB RCT studies on the effect of antidepressants for depression in patients with dementia have been published. Some studies have published positive results (Roth *et al.*, 1996;Lyketsos *et al.*, 2003), but mostly studies have published negative results (Banerjee *et al.*, 2011;Rosenberg *et al.*, 2010;Weintraub *et al.*, 2010). One study has indicated a positive effect of antidepressants for NPS, especially emotional bluntness, confusion, irritability, anxiety, fear/panic, depressed mood and restlessness (Nyth and Gottfries, 1990), but this result has not been reproduced. None of our patients had a depressive disorder at inclusion, and we ensured that patients were excluded if there was a history of depression or documented depressive disorder in the medical record of the patients. At inclusion the median score on the CSDD was 4 in the antidepressant discontinuation group (ADG) and 5 in the antidepressant continuation group (ACG), indicating no depressive disorder at inclusion. After 25 weeks the mean change in CSDD score was 2.53 (increasing depressive symptoms) in the ADG and -0.43 (decreasing depressive symptoms) in the ACG, a highly statistically significant result. Nevertheless, the CSDD scores after 25 weeks were still not an indication of a depressive disorder. Comparison of our results with studies on the effect of antidepressants for a depressive disorder is, therefore, difficult. All the same it is interesting that removing a treatment, for which there is weak evidence in the literature, significantly changes the CSDD score in the patients in a small cohort of patients.

One obvious difference between our discontinuation study and studies of the effect of antidepressants is the cohort of included patients. We included patients who had been prescribed antidepressants for more than three months, and, although the indication for prescribing the medication in the first place was poorly documented in the patients' medical records, there is a chance that the prescribing doctor had observed depressive symptoms justifying the prescription. The cohort studied for the effect of antidepressants had a documented depressive disorder at inclusion, indicating that our study cohort was

different from the study cohort in studies of the effectiveness of antidepressants for a depressive disorder.

Another explanation for divergence between the results of our study and previous studies of the effect of antidepressants for depression is the doses of antidepressant used in the different studies. In our study the mean antidepressant dosage at inclusion was 15.9 mg/day for citalopram (79.5% of defined daily dose, DDD), 25.0 mg/day for paroxetine (125% of DDD), 65.0 mg/day for sertraline (130% of DDD) and 10.6 mg/day for escitalopram (106% of DDD). In two studies on the effects of antidepressant for depression the mean sertraline dose was 70 mg/day (Banerjee *et al.*, 2011) and 90 mg/day (Rosenberg *et al.*, 2010). In the study by Nyth *et al*. patients in the treatment group received 20-30 mg citalopram per day (Nyth and Gottfries, 1990), substantially higher doses than the patients were prescribed at inclusion in our study. In conclusion, the patients in our study were prescribed lower doses of antidepressants at inclusion than patients in studies of the effectiveness of antidepressant for depression. It is unlikely that the negative effects of the described studies are caused by too high daily doses of the antidepressants, and the differences in mean daily dose of antidepressants cannot explain the disparity between the studies.

In our study we tapered out the antidepressant medication over one week in a blinded way, and discontinued the medication at day seven. This discontinuation period is shorter than clinicians would have chosen for patients in a usual nursing-home setting. Could the quick one-week discontinuation period have led to the increasing depressive symptoms in the ADG? Analysing the CSDD score, in the patients completing the 25-week study period, at the five assessments (baseline, four, seven, thirteen and twenty-five weeks), showed that the changes from baseline to the following assessments were statistically significant at assessment three (week seven), assessment four (week 13) and assessment 5 (week 25). The small increase in the mean CSDD score from 5.25 at baseline to 5.73 after four weeks in the ADG could hardly support the notion that quick discontinuation leads to increasing depressive symptoms.

The DB RCT discontinuation study we have presented is unique because it is the only discontinuation study of antidepressants in patients with dementia and NPS. The results contradict other studies, which was probably caused by differences in the study populations. The clinical interpretation of the study is that patients using antidepressive

drugs for NPS are affected by the medical treatment, and they will deteriorate if the antidepressants are discontinued. A large DB RCT study including patients not previously prescribed antidepressants for NPS should be conducted, to find evidence for the effect of antidepressants for NPS.

6.5 Methodological issues

The studies have some general methodological limitations. No aetiologic dementia diagnoses were made for the patients included in the two first studies. The classification of patients into no dementia and mild, moderate and severe dementia was based on categorical scores on the Clinical Dementia Rating Scale (CDR). However, previous studies in Norwegian nursing-home patients have revealed a good correlation between CDR scores and the dementia diagnosis based on clinical examination of the patients (Engedal, 1993;Nygaard and Ruths, 2003). For the two antidepressant discontinuation studies all patients were examined by the nursing-home clinician and an aetiological dementia diagnosis was made.

Several assessors were involved in the project. For the study on the prevalence and course of the NPS in nursing homes, the assessors were registered nurses from the nursing homes, who assessed patients in their own nursing home. In the validation study of the SIB, all patients were examined by the project leader and one registered nurse. For the pilot discontinuation study, the only assessor was the project leader, and for the DESEP antidepressant discontinuation study there were 16 study centres with minimum one to three research nurses. All assessors underwent a one-day training course, and they were all supervised during the project period. Nevertheless, there is a chance that inter-tester bias may have arisen during testing as there could have been small individual differences in the manner in which tests and assessment scales were applied to the patients, although inter-rater reliability is good for all the assessment scales used in the project.

To be able to generalise the results of the studies, the cohorts have to be representative of the general nursing-home population. To assure representativeness in the DESEP antidepressant discontinuation study, a multicentre approach with 16 study centres in 14 counties was chosen. In the remaining three studies the nursing homes were chosen for their convenience. In the validation study of the SIB effort was made to include patients with mild, moderate and severe dementia, based on the CDR score. Patients in the pilot discontinuation study, the study on the course of the NPS and the validation study of the

SIB were recruited from nursing homes in two counties (Oppland and Hedmark) situated in the south-eastern part of Norway. The counties are rural areas, comprise a few middle-sized towns and lack the multi-ethnicity found in larger cities. For the SIB validation study, the representativeness of the nursing homes is of less significance to the validity of the study, but, to be able to generalize the results in the study on the prevalence and course of the NPS in nursing homes from the studied cohort to the general nursing-home population, we should have used a more representative sample. Nevertheless our results on the course of the NPS in patients with dementia are comparable with previous studies in Norway and internationally (Selbaek *et al.*, 2007;Selbaek *et al.*, 2008;Wetzels *et al.*, 2010b), indicating that the courses of the symptoms are a result of the dementia disease itself rather than environmental factors that vary between nursing homes.

6.6 Further directions for research

Much research has been done on dementia, depression in dementia, neuropsychiatric symptoms in dementia and the treatment for different symptoms of dementia. Nevertheless, there are several topics that should be studied further.

As mentioned, a large DB RCT studying the effect of antidepressants for NPS should be conducted. The evidence for the effects of antidepressants for depression in patients with dementia is weak, and the evidence for the use of antidepressants for the treatment of NPS is virtually non-existent. Theoretically, SSRI could be effective for depressive symptoms in dementia, as decreased levels of serotonin are found in patients with AD and FTD (Salmon, 2007).

A further classification of patients with fluctuating and persistent NPS should be carried out, and studies on genetic polymorphism in patients with or without persistent NPS should be conducted. To prevent severe and persistent NPS in patients with dementia, risk factors for NPS should be identified. Therefore, longitudinal studies on patients with dementia should be carried out, preferably from MCI to severe dementia, taking into account potential biological, psychological and social triggers. Linking the NPS and dementia to diseases and symptoms earlier in life is essential to identify risk factors for dementia as well as NPS.

As the evidence for medical treatment for depression in dementia and NPS in dementia is weak, research into non-medical treatment for depression and NPS in dementia should be carried out.

There are several studies on the Quality of Life in dementia, but more studies are needed. One step would be to agree on a definition for Quality of Life in dementia. The Quality of Life in persons with dementia in relation to depression has been studied, but more studies on the relation between the treatment of depression or NPS and the Quality of Life are needed.

The concept of depression in dementia should be studied for the better understanding of the differences between depression in the elderly, depressive symptoms in patients with dementia and a depressive disease in patients with dementia. Further, studies on the treatment, both medical and psycho-social, options for depression in dementia should be conducted.

7 Conclusions

We have studied the validity and reliability of the Norwegian version of the Severe Impairment Battery (SIB). This cognitive test was found both valid and reliable when used on patients with moderate and severe dementia living in Norwegian nursing homes.

Furthermore, we studied the prevalence and the course of neuropsychiatric symptoms (NPS) in patients with dementia in Norwegian nursing homes. We found that NPS were prevalent and that most of the patients had at least one NPS at all times. The three NPS with highest cumulative prevalence were irritability (63.5%), agitation (51.0%) and disinhibition (50.0%). The individual NPS followed a fluctuating course, but delusion, agitation and irritability were the most persistent NPS. This should be taken into account when treating patients with NPS in dementia.

Finally, we conducted a DB RCT antidepressants discontinuation study in patients with dementia and NPS, but no depressive disorder. After 25 weeks the group of patients discontinuing antidepressant treatment had a significant increase in their depressive symptoms assessed by the Cornell Scale of Depression in Dementia (CSDD), compared to the group of patients continuing antidepressant medication, who had a small decrease in their depressive symptoms.

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doi:10.1017/S1041610211001177

The course of neuropsychiatric symptoms in patients with dementia in Norwegian nursing homes

Sverre Bergh,[1] Knut Engedal,[1,2,3] Irene Røen[1] and Geir Selbæk[1,2]

[1] *Centre of Old Age Psychiatric Research, Innlandet Hospital Trust, Ottestad, Norway*
[2] *Norwegian Centre of Dementia Research, Oslo University Hospital, Ullevaal, Norway*
[3] *University of Oslo, Oslo, Norway*

ABSTRACT

Background: Neuropsychiatric symptoms (NPS) are common in patients with dementia, and cause distress for patients. Studies on the prevalence, incidence, persistence and resolution of NPS in patients living in nursing homes are sparse. The aim of this study was to evaluate the course of NPS in patients with dementia living in Norwegian nursing homes.

Methods: 169 patients from seven Norwegian nursing homes were assessed five times over a period of 16 months with the Neuropsychiatric Inventory (NPI). The severity and the frequency of the NPI were analyzed.

Results: 91.7% of the patients had at least one clinically significant NPS at one or more assessments over the 16 months. Irritability (63.5%), agitation (51.0%) and disinhibition (50.0%) had the highest cumulative prevalence, while irritability (42.6%), disinhibition (37.8%) and depression (31.5%) showed the highest cumulative incidence. Delusion, agitation and irritability were enduring symptoms while the other symptoms had high resolution rates. The severity of the NPS did not vary significantly over time.

Conclusion: Almost every patient in Norwegian nursing homes had at least one clinically significant NPS over 16 months, but individual NPS show a fluctuating course. This should influence how we monitor and treat NPS in patients with dementia.

Key words: Neuropsychiatric Inventory, prevalence, incidence, resolution, persistence

Introduction

According to a recently published study, 80.5% of persons living in Norwegian nursing homes have dementia (Selbaek *et al.*, 2007). In addition to cognitive decline, neuropsychiatric symptoms (NPS) are disturbing symptoms in all dementia diseases. Of the patients with dementia in Norwegian nursing homes, 71% have at least one clinically significant neuropsychiatric symptom as measured by the Neuropsychiatric Inventory (Selbaek *et al.*, 2007). Neuropsychiatric symptoms cause distress for the patients, their relatives and nursing home staff (Sourial *et al.*, 2001), and increase the incidence of physical restraints in the nursing homes (Werner *et al.*, 1989; Kirkevold *et al.*, 2004) and the prescription of psychotropic drugs (Bartels *et al.*, 2003).

Correspondence should be addressed to: Sverre Bergh, Innlandet Hospital Trust, Post boks 68, 2312 Ottestad, Norway. Phone: +47 456 79 393; Fax: +47 625 81 401. Email: Sverre.bergh@sykehuset-innlandet.no. Received 16 Feb 2011; revision requested 29 Apr 2011; revised version received 9 May 2011; accepted 22 May 2011.

As dementia becomes more severe, the NPS occur more frequently (Selbaek *et al.*, 2007). Not surprisingly therefore, the prevalence of NPS among community-dwelling patients with dementia is lower (Lyketsos *et al.*, 2002; Aalten *et al.*, 2005; Savva *et al.*, 2009) than among patients living in nursing homes (Ballard *et al.*, 2001; Selbaek *et al.*, 2007; Zuidema *et al.*, 2007). Previous studies assessing the course of NPS have included community-dwelling patients (Devanand *et al.*, 1997; Marin *et al.*, 1997; Haupt *et al.*, 2000; Aalten *et al.*, 2005; Ryu *et al.*, 2005) and nursing home patients (Burton *et al.*, 1995; Wagner *et al.*, 1995; Ballard *et al.*, 2001; Wancata *et al.*, 2003; Selbaek *et al.*, 2008b; Wetzels *et al.*, 2010). Although the studies differ in terms of their assessment instruments, length of the follow-up period and number of assessments within the follow-up period, they have some results in common. Most of the patients with dementia have at least one neuropsychiatric symptom present at all times, but it seems that the specific NPS have a fluctuating course. Only one study on the course of NPS in

nursing home patients has a longer follow-up period than one year (Wetzels *et al.*, 2010). Therefore, there is a lack of long-term follow-up studies focusing on the course of NPS. The aim of our study was to assess the prevalence, incidence, resolution and persistence of NPS, and to study the severity of NPS with frequent assessments during a 16-month follow-up period in a group of nursing homes patients.

Methods

Patients

Patients were recruited between April 2008 and April 2010 from seven nursing homes in two counties in the south-eastern part of Norway. The seven nursing homes were non-randomly invited to take part in the study. They contain special care units and regular units and are a mix of small and big nursing homes. All 271 patients in these nursing homes were invited to take part in the study, and the inclusion criterion was that the patient or a relative consented to participation. Sixty-one patients were not included in the study, leaving 210 patients for inclusion. Of the 61 who were not included, 29 declined to participate, 25 relatives declined on behalf of the patients, two patients moved out of the nursing home before data collection commenced, one patient was in a terminal stage of life, and four patients were not asked to participate because it was deemed improper to ask for the consent by the nursing home care workers. Fifty-seven patients (27.1%) lived in a Special Care Unit (SCU) and 153 patients (72.9%) lived in Ordinary Units (OU). Of the 210 patients, 169 patients (80.5%) had dementia defined as a Clinical Dementia Rating Scale (CDR) score > 0.5. An analysis was done using data collected from these 169 patients with dementia.

Procedure and assessments

The patients were assessed every four months for 16 months, a total of five assessments (T_0–T_4) by 25 registered nurses from the nursing homes. All assessors attended a two-day course on the use of the assessment scales prior to the data collection and were experienced in administering tests to patients with dementia. The assessors interviewed professional caregivers (registered nurses or assistants) at the nursing homes, and the same assessor interviewed the same professional caregiver at each assessment. T_0 refers to the baseline assessment, while the other four assessments are referred to as T_1 to T_4, respectively. The mean time between the assessments was 140.2 days, SD 19.6 (T_0–T_1), 140.1 days, SD 22.2 (T_1–T_2), 130.7 days, SD 15.9 (T_2–T_3) and 129.7 days, SD 17.7 (T_3–T_4).

Assessments scales

The NPS were assessed with the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994). We used the 12-item version (Cummings, 1997), which includes the following neuropsychiatric symptoms: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night time behavior disturbance and appetite and eating abnormalities.

For each symptom, the severity and the frequency were scored based on a structured interview with the professional caregivers in the nursing homes. The severity (1–3 points) and frequency (1–4 points) for each symptom were multiplied to get the score for each symptom (1–12 points). A score above three on an individual symptom was defined as a clinically significant symptom (CS-NPS) (Steinberg *et al.*, 2004). The total NPI score (0–144 points) was obtained by summing the scores of the 12 symptoms. The validity and reliability of the NPI have been established (Cummings and McPherson, 2001), as have the reliability and the validity of the Norwegian version of NPI (Selbaek *et al.*, 2008a).

In addition to the NPI, the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) and the CDR (Hughes *et al.*, 1982; Berg, 1988) were administered to the patients. MMSE was used to assess the cognitive function of the patients, and CDR to assess the severity of the dementia. No etiological dementia diagnoses were established. The validity and inter-tester reliability for each assessment scale has been established.

Demographics and information on psychotropic drug use were collected from the patients' records. We used the Anatomical Therapeutic Chemical (ATC) classification system to select five groups of psychotropic drugs: antipsychotics, antidepressants, tranquilizers (sedatives and anxiolytics), cognitive enhancers and other.

Statistical analysis

Statistical analyses were performed with Statistical Package for Social Science (SPSS), version 15.0. We did an exploratory analysis, and the differences between patients with complete and incomplete data were analyzed with independent student's t-test and χ^2 test for continuous and categorical data, respectively. Non-parametric statistics were used for non-normally distributed data. We calculated point prevalence, cumulative prevalence, incidence, cumulative incidence, and persistence

and resolution rates for each of the 12 items of the NPI. Point prevalence is the proportions of patients with a CS-NPS at each assessment, and cumulative prevalence is the proportions of patients with a CS-NPS on at least one of the five assessments. Incidence is the proportion of patients who were symptom free at one assessment, but developed a CS-NPS at the next assessment. Cumulative incidence is the proportion of patients who were symptom free at baseline but developed a CS-NPS at one of the following assessments. Persistence is the ratio of residents with CS-NPS at follow-up to residents with CS-NPS at the previous assessment, and resolution is the ratio of residents without CS-NPS at follow-up to the residents with CS-NPS at the previous assessment. To analyze the variation in severity of the NPI over time, we used the linear multiple level model (MLM). MLM is a good statistic technique for analyzing hierarchically data with repeated assessments, also when data are missing (Field, 2009).

Ethical and legal considerations

Patients or their next of kin gave their informed consent, depending on the severity of the patient's dementia. The study was approved by the Regional Ethics Committee for Medical Research in South-Eastern Norway and by the Data Inspectorate and the Norwegian Directorate of Health.

Results

Demographic characteristics

Table 1 shows the demographic data of the included patients at baseline (T_0). The number of patients lost to follow-up were 19 (11.2%), 37 (21.9%), 53 (31.3%) and 73 (43.2%) for assessments two to five (T_1–T_4), respectively. Sixty-eight patients (40.2%) died during the follow-up period and five patients (3.0%) moved to another nursing home. Premature discontinuations from the study due to moving to another nursing home were at 3, 12, 19, 24 and 36 weeks. The mean age of the included patients was 84.9 years (SD 6.7), 69.2% were women and the median length of stay in the nursing home was 673 days, minimum 28 days and maximum 6087 days (inter-quartile range, IQR, 249–1372). For the 61 patients not included in the study, their mean age was 84.9 years (SD 9.9), 63.9% were women and the median length of stay was 658 days (IQR 314–1568). The age, the gender, the length of the stay and the NPI score were not significantly different in the two groups. The average MMSE score at baseline was 14.5 (SD 6.0). The group of patients who completed the five assessments had an MMSE score of 15.3 (SD 6.1) at baseline and the group of patients who did not complete the five assessments had a MMSE score of 13.0 (SD 5.7) ($p<0.05$). Regarding the use of psychotropic drugs we found a statistical difference between the groups: 90.4% of patients lost to follow-up and 78.1% of the completers used at least one psychotropic medication, $p = 0.033$. The groups also differed in terms of CDR with the group of patients who completed five assessments having a significantly lower CDR score ($p<0.05$).

Prevalence and cumulative prevalence rates

Table 2 shows the prevalence and the cumulative prevalence rates of the individual CS-NPS. The prevalence of any CS-NPS varied between 62.9% and 72.0% over the five assessments. The three most prevalent CS-NPS were irritability, agitation and apathy (T_0 and T_1), irritability, agitation and disinhibition (T_2 and T_3) and depression, disinhibition and irritability (T_4). The three CS-NPS with the highest cumulative prevalence were irritability (63.5%), agitation (51.0%) and disinhibition (50.0%). In all, 91.7% of the patients had at least one CS-NPS at one or more assessments over the 16 months.

Incidence and cumulative incidence rates

The incidence and the cumulative incidence rates are shown in Table 3. The NPS with the highest incidence rate were irritability, apathy and agitation (T_0–T_1) disinhibition, irritability and apathy (T_1–T_2), irritability, delusions and aberrant motor behavior (T_2–T_3) and irritability, apathy and agitation (T_3–T_4). Irritability (42.6%), disinhibition (37.8%) and depression (31.5%) showed the highest cumulative incidence.

Persistence and resolution

The persistence and the resolution rates of the CS-NPS are shown in Table 4. The three CS-NPS with the highest persistence rates were agitation, irritability and disinhibition for the first (T_0–T_1) and second (T_1–T_2) follow-up period. For the third (T_2–T_3) follow-up period disinhibition, apathy and irritability showed highest persistence rates, while for the last follow-up period (T_3–T_4) the three CS-NPS with the highest persistence rates were hallucination, depression and anxiety. On the other hand, the three CS-NPS with the highest resolution rates were euphoria, eating change and night-time behavior (T_0–T_1) and (T_1–T_2), eating change, hallucination and delusion (T_2–T_3) and eating change, euphoria and apathy (T_3–T_4).

Table 1. Demographic characteristics at baseline for all included patients, patients completing the study period and patients lost-to-follow up, with statistical comparison of patients with and without complete data

	TOTAL GROUP n = 169	PATIENTS LOST TO FOLLOW UP n = 73	PATIENTS WITH COMPLETE DATA n = 96	p-value
Age in years - mean (SD)[a)]	84.9 (6.7)	85.6 (5.6)	84.4 (7.4)	0.538
Female gender (%)[b)]	117 (69.2)	56 (76.7)	61 (63.5)	0.066
Length of stay in days - median (IQR)[c)]	673 (249–1372)	746 (343–1451)	623 (169–1335)	0.211
CDR = 1 (%)[b)]	35 (20.7)	8 (6.8)	27 (28.1)	0.016
CDR = 2 (%)	63 (37.3)	28 (38.4)	35 (36.5)	
CDR = 3 (%)	71 (43.4)	37 (50.7)	34 (35.4)	
MMSE - mean (SD)[a)]	14.5 (6.0)	13.0 (5.7)	15.3 (6.1)	0.045
NPI – one or more symptoms (%)[b)]	154 (91.1)	70 (95.9)	84 (87.5)	0.839
NPI - one or more clin. sign. symptoms* (%)[b)]	119 (70.4)	52 (71.2)	67 (69.8)	0.193
Use of psychotropic drug (%)[b)]	141 (83.4)	66 (90.4)	75 (78.1)	0.033
Use of antidepressants (%)[b)]	72 (42.6)	34 (46.6)	38 (39.6)	0.363
Use of antipsychotic (%)[b)]	37 (21.9)	19 (26.0)	18 (18.8)	0.257
Use of tranquilizers (%)[b)]	94 (55.6)	40 (54.8)	54 (56.3)	0.850
Use of cognitive enhancers (%)[b)]	35 (20.7)	16 (21.9)	19 (19.8)	0.372
Use of any other psychotropic drug (%)[b)]	18 (10.7)	6 (8.2)	12 (12.5)	0.735

CDR = Clinical Dementia Ratio, MMSE = Mini Mental State Examination, NPI = Neuropsychiatric Inventory, IQR = Interquartile Range.
SD = Standard Deviation.
* Clinical Significant Neuropsychiatric Symptoms = NPI > 3.
[a)] Independent Student's t-test, [b)] Pearson Chi-square test [c)] Mann-Whitney U test.

Table 2. Prevalence and cumulative prevalence of Clinically Significant Neuropsychiatric Symptoms* (%)

SYMPTOMS	CUMULATIVE PREVALENCE T_0 - T_4	T_0 n = 169 PREV[1]	T_1 n = 150 PREV[2]	T_2 N = 132 PREV[3]	T_3 N = 116 PREV[4]	T_4 N = 96 PREV[5]
Delusion	44.9	25.5	23.4	26.2	26.1	26.1
Hallucination	17.7	12.0	11.2	10.4	9.7	7.8
Agitation	51.0	32.3	34.9	32.1	27.0	29.2
Depression	45.8	20.4	21.3	17.1	21.4	29.3
Anxiety	35.4	20.0	20.9	21.3	14.9	18.3
Euphoria	18.7	5.4	3.4	3.1	7.0	8.3
Apathy	44.8	25.9	28.0	26.6	26.3	22.1
Disinhibition	50.0	16.5	22.4	32.3	31.0	29.5
Irritability	63.5	35.1	36.9	37.2	36.2	37.2
Ab motor behaviour	45.8	23.6	21.5	22.1	23.7	16.8
Night time behaviour	32.3	13.7	14.2	14.6	15.7	16.8
Eating change	32.3	13.3	7.4	13.0	10.6	12.6
At least one CS-NPS*	91.7	70.4	72.0	70.5	62.9	68.8

* Clinically Significant Neuropsychiatric Symptoms = NPI > 3.
T_0 = Baseline/first assessment, T_1 = second assessment, T_2 = third assessment, T_3 = fourth assessment, T_4 = fifth assessment.
[1, 2, 3,4 and 5] Prevalence among all patients completing the first, second, third, fourth and fifth assessment, respectively.

Severity over time

We calculated the multilevel linear models statistics for the first-, second- and third-order polynomial growth curve of the individual NPI items. Analysis of the severity of the individual NPI items over time did not show significant differences for individual NPI items, reported as the linear, quadratic or cubic trend best describing the pattern of the data over time: delusion $F(1, 287.92) = 0.59$, $p = 0.44$; hallucination $F(1, 300.73) = 1.09$, $p = 0.28$; agitation $F(1, 319.15) = 2.47$, $p = 0.12$; depression $F(1, 277.67) = 2.71$, $p = 0.10$; anxiety $F(1, 310.78) = 0.20$, $p = 0.65$; euphoria $F(1, 311.39) = 0.57$, $p = 0.45$; apathy $F(1, 284.70) = 1.53$,

Table 3. Cumulative incidence and Incidence of Clinically Significant Neuropsychiatric Symptoms* (%)

SYMPTOMS	CUMULATIVE INCIDENCE T_1 - T_4	INCIDENCE n = 150 T_0-T_1	INCIDENCE n = 132 T_1-T_2	INCIDENCE N = 116 T_2-T_3	INCIDENCE N = 96 T_3-T_4
Delusion	26.6	11.2	13.5	14.3	12.3
Hallucination	10.8	5.0	5.5	5.1	2.4
Agitation	24.2	13.7	11.0	10.0	14.1
Depression	31.5	11.0	7.4	12.0	12.7
Anxiety	22.4	10.7	13.1	4.4	6.5
Euphoria	13.3	2.9	3.2	5.4	5.7
Apathy	27.8	17.6	13.8	9.8	13.3
Disinhibition	37.8	13.6	18.8	9.3	11.6
Irritability	42.6	18.5	14.1	16.4	17.7
Ab motor beh.	27.5	9.4	12.4	13.0	2.9
Night time beh.	21.3	9.6	9.8	7.3	8.8
Eating change	22.0	3.1	10.7	7.1	9.5
At least one CS-NPS*	82.9	44.2	32.4	19.4	40.4

* Clinically Significant Neuropsychiatric Symptoms = NPI > 3.
T_0 = Baseline/first assessment, T_1 = second assessment, T_2 = third assessment, T_3 = fourth assessment, T_4 = fifth assessment.

p = 0.22; disinhibition $F(1, 297.89) = 0.21$, p = 0.65; irritability $F(1, 283.85) = 0.02$, p = 0.90; aberrant motor behavior $F(1, 276.72) = 1.33$, p = 0.25; night-time behavior $F(1, 311.90) = 2.22$, p = 0.14; and eating change $F(1, 296.62) = 0.32$, p = 0.57.

Use of psychotropic drugs

Of the 169 patients analyzed in the study, 83.4% used at least one psychotropic drug on a daily basis at the baseline registration; 42.6% used an antidepressant, 21.9% used an antipsychotic, 55.6% used a tranquilizer and 20.7% used a cognitive enhancer.

Of the 96 patients completing the five assessments, 82 (85.4%) used one or more psychotropic drug at least at one assessment. Sixty-two out of the 90 patients (75.6%) had a persistent use as they used at least one psychotropic drug at four or five out of five assessments. Tranquilizers were the group of psychotropic drug most frequently prescribed. Sixty-three out of 97 patients (75.6%) used a tranquilizer at least at one of the assessments during the follow-up period, and 37 of these 63 (58.7%) used a tranquilizer at four or five assessments during the period. Thirty-two out of 96 patients (33.3%) used an antipsychotic at least at one assessment, and 10 of these 32 (31.3%) used the antipsychotic at four or five assessments. Fifty out of the 96 patients (52.1%) used an antidepressant at least at one assessment during the follow-up period, and 26 of these 50 (52.0%) used the antidepressant at four or five assessments.

Discussion

We report the prevalence, incidence, persistence and resolution of neuropsychiatric symptoms of patients living in Norwegian nursing homes. Our cohort consisted of 210 patients (from a total of 271) living in seven nursing homes. Of these, 169 patients had dementia according to a CDR rating of 1 and above, and results from these patients were analyzed.

Prevalence

We found that irritability, agitation and disinhibition are the most prevalent NPS in nursing homes, which correspond to other studies (Ballard *et al.*, 2001; Selbaek *et al.*, 2007; Wetzels *et al.*, 2010). In contrast, apathy, depression and aberrant motor behavior are found to be more prevalent among outpatients (Aalten *et al.*, 2005). Owing to differences in assessment instruments, the studies by Wancata *et al.* (2003) and Wagner *et al.* (1995) are difficult to compare with ours, but Wancata *et al.* report a cumulative prevalence over six months of depression 32.6%, delusion 9.3% and hallucination 2.4%. The studies by Aalten *et al.* (2005) and Wetzels *et al.* (2010) are comparable to our study using the same design, following a cohort of patients with dementia over five consecutive assessments with the NPI. However, the two Dutch studies differ from our study as the time between each assessment in their studies was six months not four. We report that the cumulative prevalence of any CS-NPS over 16 months is 91.7% compared to 96.6% in a nursing home population in the Netherlands

Table 4. Persistence and resolution of Clinically Significant Neuropsychiatric Symptoms* (%)

	T_0 - T_1		T_1 – T_2		T_2 – T_3		T_3 – T_4	
SYMPTOMS	PERSISTENCE	RESOLUTION	PERSISTENCE	RESOLUTION	PERSISTENCE	RESOLUTION	PERSISTENCE	RESOLUTION
Delusion	57.9	42.1	65.5	34.5	55.2	44.8	65.2	34.8
Hallucination	58.8	41.2	50.5	49.5	54.5	45.5	100.0	0.0
Agitation	73.1	26.9	68.8	31.2	65.7	34.3	75.0	25.0
Depression	66.7	33.3	51.7	48.3	63.2	36.8	85.0	15.0
Anxiety	60.7	39.3	50.0	50.0	61.9	38.1	80.0	20.0
Euphoria	12.5	87.5	0.0	100.0	66.7	33.3	42.9	57.1
Apathy	56.4	43.6	61.8	38.2	70.0	30.0	52.6	47.4
Disinhibition	66.7	33.3	73.3	26.7	77.8	22.2	79.2	20.8
Irritability	67.9	32.1	74.0	26.0	69.0	31.0	75.0	25.0
Ab motor behavior	57.1	42.9	53.6	46.4	68.2	31.8	60.9	39.1
Night time behavior	39.1	60.9	47.1	52.9	55.6	44.4	64.3	35.7
Eating change	36.8	63.2	40.0	60.0	33.3	66.7	37.5	62.5
At least one CS-NPS*	83.2	16.8	85.3	14.7	82.5	17.5	89.3	10.7

* Clinically Significant Neuropsychiatric Symptoms = NPI > 3.
T_0 = Baseline/first assessment, T_1 = second assessment, T_2 = third assessment, T_3 = fourth assessment, T_4 = fifth assessment.
Persistence = ratio of residents with CS-NPSs at follow up to residents with CS-NPSs at the previous assessment.
Resolution = ratio of residents without CS-NPSs at follow up to the residents with CS-NPSs at the previous assessment.

(Wetzels *et al.*, 2010). When looking at single NPI symptoms, Wetzels *et al.* report that delusion, hallucination, depression and disinhibition are approximately half as prevalent as we report in our study. In the study by Aalten *et al.* (2005) on Dutch outpatients they reported similar figures to ours on the cumulative prevalence of individual clinically significant NPS. Our drop-out rate was 43.2%, caused by death (68 patients) and moving from the nursing home (five patients). Aalten *et al.* (2005) reported a drop-out rate of 50%, with 24% due to death and 26% refusing to participate. Wetzels *et al.* (2010) reported a drop-out rate of 60% (54% due to death and 6% moving to another nursing home). At inclusion our patients had a mean MMSE score of 14.5 points, whereas those in the study by Aalten *et al.* (2005) had a mean MMSE score of 18.1 (SD 4.7) and those in the study by Wetzels *et al.* (2010) had a mean MMSE score of 7.6 (SD 7.1). These MMSE differences and the differences in drop-out rates should be regarded as a possible explanation for the difference in the results. The follow-up periods in their studies was eight months longer than in our study, with the same number of assessments, which also could explain the difference in the results. In addition, pharmacological treatment and non-pharmacological interventions could also have influenced the results of the three studies, but we do not have sufficient information of such variables to make any conclusions. In our study the nursing homes received extra attention from the department of Old Age Psychiatry during the study. They were given extensive information on dementia and the different assessment scales. Parallel with the assessment of the NPS the nursing homes were encouraged to create their own small research project to improve the quality of their care. This extra attention might therefore have improved the quality of care in the nursing homes, which could explain some of the differences between our study and other similar studies.

Incidence

We report that irritability (42.6%), disinhibition (37.8%) and depression (31.5%) showed the highest cumulative incidence. A previous Swiss study has reported an incidence after six months of 10.5% for depression, 4.7% for delusion and 0.0% for hallucination (Wancata *et al.*, 2003), while a previous Norwegian study reported that agitation, apathy and irritability have the highest cumulative incidence after one year (Selbaek *et al.*, 2008b). This result was confirmed in the study from the Netherlands by Wetzels *et al.* (2010), which also found that depression (19.6%) and disinhibition (16.7%) had a fairly low cumulative incidence. Why this

difference? Selbæk and colleagues report data for a large number of patients on two assessments over one year, but do not have information on the symptoms experienced by the patients between the two assessments. Both Wetzels' study and our own have a remarkably higher cumulative incidence rate than that reported by Selbæk and colleagues, indicating that the NPS show a rapid cycling in their course. The study by Wetzels and colleagues was based on patients with dementia living in Special Care Units (SCU), and their dementia was more severe than in other studies. As the dementia progresses the presentation of the NPS changes. This could contribute to the differences between the studies. Delusion, hallucination, agitation/aggression, apathy, disinhibition and aberrant motor behavior all significantly increase in frequency with more severe dementia (Selbaek *et al.*, 2007).

Persistence, resolution and possible influence of psychotropic drug use

In our study delusions, agitation, depression, disinhibition, irritability and aberrant motor behavior showed high persistence over the five assessments, which correspond with the results from a previous study on nursing home patients who reported agitation/aggression and aberrant motor behavior to be the most persistent NPS (Wetzels *et al.*, 2010). In the Swiss study (Wancata *et al.*, 2003), depression was persistent in 63.3%, delusion in 50.0% and hallucination in 50.0%. In outpatients, depression, apathy and aberrant motor behavior were the NPS with highest persistence (Aalten *et al.*, 2005). Compared to the two Dutch studies it seems that patients with dementia living at home differ in their symptom expression from the nursing home patients with dementia. This difference could be due to dementia severity, but also to environmental factors, caregiver burden and pharmacological and non- pharmacological interventions (Rozzini *et al.*, 2006).

We noted that the use of psychotropic drugs was very common among our study subjects; 83.4% of them used at least one psychotropic drug at one assessment during the 16 months period. Almost 76% of the patients used one or more psychotropic drugs at four or five out of the five assessments. We did not specifically compare the persistent use of psychotropic drugs with the persistence of the CS-NPS. However, as the persistent use of psychotropic drugs generally is very high, we assume that the persistence of NPS is not influenced to a significant degree by the drug use. According to the results of two previous studies of nursing home patients, the severity of dementia and factors associated with being institutionalized most probably explain the persistence of the NPS (Selbaek *et al.*, 2008b; Wetzels *et al.*, 2010).

Severity over time

We did not find any significant change in the severity of the NPS during the 16-month follow-up period. This contradicts the findings of Aalten *et al.* (2005) in their two-year study of NPS in outpatients and Wetzels *et al.* (2010) in their nursing home cohort. Aalten *et al.* reported significantly decreased severity of depression and increased severity of aberrant motor behavior and apathy, while Wetzels *et al.* reported significant reduction in depression and anxiety. We do not know how to explain these contradictory findings, although differences in statistical methods may play a role. Wetzels *et al.* used Friedman test to analyze change in NPI severity score over time, whereas Aalten *et al.* used analyses of variance (ANOVA) with repeated measurements; in our study we used the Multiple Level Method.

Clinical implications and treatment options

Our study confirms the findings from previous studies. Most of the patients with dementia, living either in nursing homes or in their own homes, will experience at least one NPS over the course of 16 to 24 months. Individual symptoms have a fluctuating course, with high resolution and incidence rate throughout the period. As clinicians we should monitor our patients well, with repeated assessments with the NPI or another systematic tool for the NPS. In the same way as we monitor the blood sugar and adjust the treatment in patients with Diabetes Mellitus we should monitor and adjust the treatment in patients with dementia and NPS. According to our results, delusion, hallucinations, disinhibition, agitation and irritability have a resolution rate between assessments varying from 30 to 40%, indicating that approximately one-third of the patients with these symptoms are symptom-free four months later. At the same time, we know that 75% of patients with dementia using an antipsychotic are still prescribed the same antipsychotic 12 months later (Selbaek *et al.*, 2008b). We see the same trend concerning the symptoms of depression, anxiety, apathy and irritability. The resolution rates for these symptoms are between 26% and 50% while the persistence rates for antidepressant prescription is 79.2% over 12 months (Selbaek *et al.*, 2008b).

There are several weaknesses in the present study. The nursing homes taking part in the study were a convenience sample of nursing homes from the south-eastern part of Norway. There was no randomization or stratification when inviting

nursing homes to take part in the study, and the patients in our study may not be representative of the Norwegian nursing home population. In fact, we believe that the nursing homes taking part in the study were among the better nursing homes in the region, according to their knowledge of, education and interest in dementia. It is likely that knowledge of and interest in dementia among the professional caregivers in the nursing homes will reduce NPS among the nursing home residents, and our study may underestimate the prevalence of NPS in Norwegian nursing homes. Dementia was diagnosed based on a CDR scale score of 1, 2 or 3, but we did not make any etiological dementia diagnosis which could improve the quality of our study. We were therefore unable to perform regression analysis adjusted for dementia diagnosis; however, previous studies have demonstrated that staging dementia based on the CDR score is a valid substitute for a dementia diagnosis (Nygaard and Ruths, 2003). We did not make any adjustments for use of psychotropic drugs and somatic or psychiatric comorbidity, nor did we adjust for differences in nursing staff and type of ward in the nursing homes. The patients were assessed by several assessors, and although they all attended a two-day training course and the Norwegian version of the NPI has been found to have good inter-rater reliability, the relatively high number of assessors could bias the results. Almost all the patients lost to follow-up died during the follow-up period, and as shown in the analysis, the patients lost to follow-up had significantly more severe dementia than the patients completing the follow-up period. In our study, as well as in other studies (Selbaek *et al.*, 2008b;Wetzels *et al.*, 2010), changes in symptoms may partly be due to the Hawthorn effect whereby the symptoms of the patients taking part in the study can improve just because they are taking part (Roethlisberger *et al.*, 1939).

The strength of our study is the relatively large number of included patients, and the relatively low drop-out rate (43.2%) compared to other nursing home studies. We made assessments of the patients every four months, a shorter interval than other reported studies.

Conclusion

We report a high prevalence of neuropsychiatric symptoms in Norwegian nursing homes. Only 8% of the patients did not experience a CS-NPS over the 16-month follow-up period. The most prevalent NPS were irritability, agitation and disinhibition, and these also had the highest persistence. Most of the NPS are fluctuating in their course, and very few symptoms are present continuously for more than eight months.

Conflict of interest

None.

Description of authors' roles

Sverre Bergh took part in the design of the study, did all the statistical analysis and wrote the paper. Irene Røen took part in designing the study, the data collection and approved the manuscript. Knut Engedal and Geir Selbæk took part in designing the study and writing the paper.

Acknowledgments

The study was supported by unrestricted grant from the Norwegian Medical Association.

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III

IV

A double blind, randomized placebo controlled discontinuation trial of antidepressants in persons with dementia and neuropsychiatric symptoms – the DESEP study

Journal:	*BMJ*
Manuscript ID:	Draft
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
Complete List of Authors:	Bergh, Sverre; Innlandet Hospital Trust, Centre for Old Age Psychiatric Research Selbøk, Geir; Innlandet Hospital Trust, Norway, Centre for Old Age Psychiatric Research Engedal, Knut; Oslo University Hospital, The Norwegian Centre for Dementia Research; University of Oslo, Medicine
Keywords:	antidepressant, discontinuation, dementia, neuropsychiatric symptoms

A double blind, randomized placebo controlled discontinuation trial of antidepressants in persons with dementia and neuropsychiatric symptoms – the DESEP study

Sverre Bergh[1], MD, Geir Selbæk[1,2], MD PhD, Knut Engedal[1,2,3]MD PhD

[1]Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, N-2312 Ottestad, Norway Sverre Bergh Researcher, Geir Selbæk Head of Research Department [2] The Norwegian Centre for Dementia Research, Oslo University Hospital, Ullevaal, 0424 Oslo Norway [3] The University of Oslo, 0316 Oslo, Norway Knut Engedal Professor

Correspondence to: Sverre Bergh, sverre.bergh@sykehuset-innlandet.no

Clinical trial: NCT00594269

EudraCT number: 2006-002790-43

Running title: Discontinuation of antidepressants in patients with dementia

Key words: antidepressant, discontinuation, dementia, neuropsychiatric symptoms

Background: Forty percent of nursing home residents in Norway are prescribed antidepressants, but the indications for their use are often unclear. The evidence for the efficacy of antidepressants for Neuropsychiatric Symptoms (NPS) is weak.

Methods: A twenty-five week double-blind antidepressant discontinuation RCT was performed, on nursing-home residents with dementia and NPS, without a depressive disorder. The primary outcomes were changes on the Cornell Scale of Depression in Dementia (CSDD) and the 10-items version of the Neuropsychiatric Inventory (NPI) after 25 weeks, while secondary outcomes were changes on the Clinical Dementia Rating Scale, the Unified Parkinson Disease Rating Scale, the Quality of Life – Alzheimer Disease, the Lawton & Brody's Physical Self-Maintenance scale and the Severe Impairment Battery.

Results: There was a significantly different mean change between baseline and 25 weeks between the two groups in the CSDD score, 2.53 (SD 5.61, worsening) in the antidepressant discontinuation group (ADG) and minus 0.43 (SD 3.61) in the antidepressant continuation group (ACG), p=0.001. The mean total score for the NPI-10 increased by 5.93 (SD 19.41, worsening) in the ADG and decreased by 1.39 (SD 15.26) in the ACG, p=0.023. A non-response analysis (>30% worsening on the CSDD) confirmed these results, as significantly more patients in the ADG (22.0%), worsened compared to the ACG (10.3%), p=0.006. No statistically significant differences between the groups were found for secondary outcomes.

Conclusions: Patients in the ADG experienced more depressive symptoms assessed by the Cornell Scale of Depression in Dementia and more NPS assessed with the Neuropsychiatric Inventory.

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Background: Almost 80% of nursing-home residents in Norway have dementia, and 90% of them have one or more Neuropsychiatric Symptoms (NPS).[1] The individual NPS in patients with dementia fluctuate, and the prevalence of the NPS differs according to the dementia diagnosis and the severity of the dementia.[2,3] Non-pharmacological interventions are the treatments of choice for NPS, but if the symptoms persist a pharmacological approach should be tried.[4] In a review article Sink et al. identified four RCTs reporting the effect of antidepressants on NPS.[5] One study reported a statistically significant effect after 12 weeks treatment [6], the remaining studies were negative. A Cochrane review came to the same conclusion.[7] A recent review article summarized nineteen RCTs comparing antidepressants with antipsychotics or a placebo for NPS in dementia.[8] Eleven studies recognized that antidepressants were effective in treating NPS.

The effect of antidepressants on depression in patients with dementia has been studied in many RCTs of varying quality, summarized in meta-analyses.[9,10] They show a trend towards antidepressant

effectiveness, but the most recent meta-analysis could not confirm the efficacy of antidepressants on depression in patients with dementia.[9] a result supported by a Cochrane review and a recent RCT showing no effect of sertraline and mirtazepine over placebo for depression in dementia.[10,11]

About 40% of residents in Norwegian nursing homes are prescribed antidepressants for long term use.[1] Approximately 50% of them are prescribed a Selective Serotonin Reuptake Inhibitor (SRRI), but the indication for the prescription is unclear.[12] The SSRIs have been used for patients with dementia because of their favourable side effect profile, a profile questioned by a recent study.[13] Therefore, we wanted to study the effects of the discontinuation of four different SSRIs with regard to depressive symptoms, NPS and side-effects in patients with dementia living in Norwegian nursing homes.

METHODS

STUDY DESIGN

The study was a 25-week double-blind parallel group randomized placebo controlled discontinuation trial of four SSRIs, carried out independently of any pharmaceutical company. The first week after baseline assessment, the antidepressants were either tapered off and replaced by a placebo (antidepressant discontinuation group, ADG) or replaced by a study drug containing active medication (same kind and same dose) as before inclusion (antidepressant continuation group, ACG). The trial was registered in ClinicalTrial.gov on January 3th 2008 (NCT00594269).

RANDOMIZATION AND MASKING

The computer generated randomization (1:1) in blocks of four and packing of study medication was done at the Hospital Pharmacy, Innlandet Hospital Trust, and was kept hidden from the participants, the caregivers and the assessors until the completion of the data collection and the statistical analyses. Randomization was done across study centres and facilities.

PATIENTS

Participants were nursing home residents (men and women), recruited from sixteen study centres in Norway. Inclusion criteria were patients with a diagnosis of dementia in Alzheimer Disease (AD), Vascular Dementia (VaD) or mixed AD/VaD (as defined in the International Classification of Diseases, version 10, diagnostic criteria for research), nursing home residents for more than four weeks, and prescriptions of an SSRI for at least three months. Exclusion criteria were a clinical history of a depressive disorder or schizophrenia, severe somatic disease or terminal illness, or being unable to take tablets/capsules as prescribed. No changes in the dose of the current antidepressant medication were allowed in the last four weeks before inclusion and throughout the study period. Changes in the prescription of psychotropic drugs other than antidepressants during the study period were allowed. The participants (if competent) or their next of kin (legally representing if no kin) gave their informed written consent.

ASSESSMENTS AND OUTCOMES

The project leader and the project coordinator trained all the research nurses in a one-day training course, learning about the study protocol and the questionnaires. A geriatric psychiatrist or general practitioner trained in geriatric psychiatry studied the participants' medical records and if necessary examined the patient, to ensure correct diagnosis of dementia and to ensure exclusion of patients with a depressive disorder. The research nurses collected all the data from the nursing homes, closely supervised by the project leader and the project coordinator to ensure a reliable data collection. The degree of dementia, cognitive impairment, extra pyramidal side-effects (EPS) and the level of function were assessed at baseline and after twenty-five weeks with the Clinical Dementia Rating Scale (CDR),[14] the Severe Impairment Battery (SIB),[15] the Unified Parkinson Disease Rating Scale (UPDRS, six-item version)[16], and the Lawton & Brody's Physical Self-Maintenance scale (PSMS),[17] respectively. The CDR scale is a six-item questionnaire staging the severity of the dementia

in no dementia (CDR=0), possible dementia (CDR=0.5), mild (CDR=1), moderate (CDR=2) or severe dementia (CDR=3). The SIB is a cognitive test with 51 items (minimum score zero, maximum score 100), especially developed for patients with moderate and severe dementia.

Efficacy assessments were made at baseline, and at four, seven, thirteen, and twenty-five weeks. Primary endpoints were changes in the Cornell Scale for Depression in Dementia (CSDD)[18] and the Neuropsychiatric Inventory (NPI)[19] after twenty-five weeks. The CSDD (minimum score zero, maximum score thirty-eight) assesses the depressive symptoms of the patients with dementia. A score of eight points and above is regarded as a sign of a depressive disorder, while a score of thirteen and above is regarded as a sign of a severe depressive disorder.[20] The CSDD was divided into two sub-scales, mood (sadness, anxiety, pessimism, suicidal thoughts, poor self esteem and delusion) and non-mood (the remaining 13 symptoms), according to a recent Norwegian factor analysis.[21] The NPI 10-item version assesses the NPS, and includes the sub-items; delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition and aberrant motor behaviour. For each item the frequency (1-4 points) and the severity (1-3 points) of the symptoms is scored. The frequency and the severity scores are multiplied, a score ≥4 is regarded as a clinically relevant symptom and a score ≥9 is regarded as a severe symptom.[22] The NPI was divided into the following sub-syndromes: Affective (NPI-depression and NPI-anxiety), Psychosis (NPI-hallucinations and NPI-delusions), Agitation (NPI-agitation, NPI-irritability and NPI-disinhibition) and Apathy (NPI-apathy).[23]

The secondary endpoints were changes after twenty-five weeks on the UPDRS, the Quality of Life – Alzheimer Disease (QoL-AD)[24], the PSMS, the SIB and the CDR. SIB was administered to the patients unless they were unable to communicate or refused testing. The QoL-AD was administered to both the patients and the caregivers. The additional assessments were administered to one of the nurses at the nursing home.

STATISTICAL ANALYSIS

The power calculation was based on the only published pilot study on the discontinuation of antidepressant in persons with dementia.[25] Based on a statistical power of 80%, a two-tailed significance level of 0.05 and a drop-out rate of 33%, 45 patients had to be included in each group to ensure enough statistical power to detect a 30% change in the CSDD score. The corresponding numbers were 76 patients in each group to detect a 30% change in the NPI score. We had planned to enroll 152 patients in the study, but the inclusion rate was too slow, and only 128 patients were included.

All the included patients were analyzed in the safety analysis, and all the patients with at least one assessment after the baseline (117 patients) were included in the efficacy analysis. The last-observation-carried-forward method was used to impute values if follow-up data were missing. We also analyzed the patients with complete data (n=81) for changes in the primary endpoints, presented as observed cases. Assessment scales which lacked more than 20% of the data were not analyzed. Analyses were done across study centres without sub-analyses of each study centre, as ten study centres were small (<ten patients).

Statistical analyses were performed in the Statistical Package for Social Science (SPSS), version 15.0. The baseline characteristics were analyzed with the independent Student's t-test for parametric data, Mann–Whitney-U test for non-parametric data and chi-square statistics or Fischer's exact test for categorical data. The two study groups were compared with an independent Student's t-test for the difference between baseline and 25 weeks for the two primary outcomes; CSDD and NPI.

ETHICS, MONITORING, GRANTS, AND PLACEBO FORMULATION

The study was approved by the Norwegian Medicines Agency, the Regional Committee of Medical Research Ethics and the Norwegian Directorate of Health. It was conducted according to the standard of Good Clinical Practice (GCP), and monitored by independent persons from Oslo University Hospital. The procedures were conducted in accordance with the Helsinki Declaration as revised in 1983.

The study was funded by unrestricted grants from the Innlandet Hospital Trust, the Research Council of Norway and the South-Eastern Norway Regional Health Authority. H. Lundbeck A/S provided the study with escitalopram tablets and placebos free of charge (56% of the patients), but with no obligations for publication. Encapsulated tablets for the remaining three antidepressants and corresponding placebo capsules containing only inert filler were purchased from Catalent Pharma Solutions, Bolton, UK.

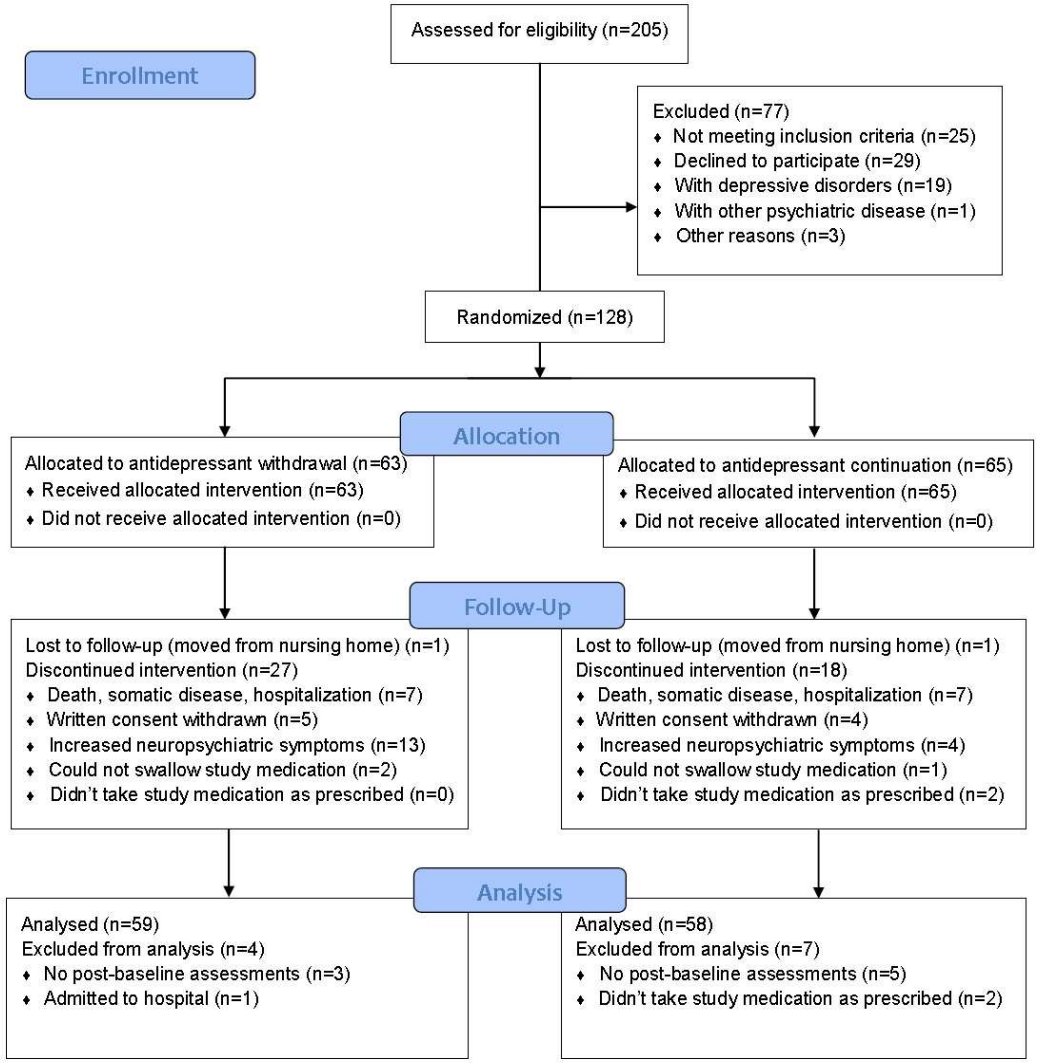

Figure 1: Flow chart

Table 1. Demographic characteristics at baseline for all included patients (n=128), with statistical analysis of differences between antidepressant discontinuation group (ADG) and antidepressant continuation group (ACG).

	ADG n = 63	ACG n = 65	p-value
Age in years - mean (SD) [a)]	85.3 (8.2)	86.1 (6.7)	0.543
Female gender (%) [b)]	49 (77.8)	47 (72.3)	0.475
Diagnosis [b)]			
AD (%)	32 (50.8)	38 (58.5)	0.193
VaD (%)	16 (25.4)	10 (15.4)	0.159
Mixed AD/VaD (%)	15 (23.8)	17 (26.2)	0.759
Clinical Dementia Rating [b)]			
CDR = 1 (%)	8 (12.5)	8 (12.3)	0.947
CDR = 2 (%)	32 (50.0)	31 (47.7)	0.726
CDR = 3 (%)	23 (35.9)	26 (40.0)	0.684
SIB - median (IQR) [c)]	78 (64.5 - 91.5) n=50	81 (68 - 94) n=52	0.721
- mean (SD)	72.5 (19.5)	70.9 (25.6)	
CSDD - median (IQR) [c)]	4 (1.5 - 6.5) n=61	5 (1.5 - 8.5) n=64	0.278
- mean (SD)	5.03 (4.15)	5.89 (4.62)	
CSDD - mood - median (IQR) [c)]	1 (0 - 2) n=63	1 (-1 - 3) n=64	0.228
- mean (SD)	1.28 (1.71)	1.95 (2.40)	
CSDD - non Mood - median (IQR) [c)]	3 (1 - 5) n=62	2.5 (0 - 5) n=64	0.931
- mean (SD)	3.44 (3.30)	3.32 (2.90)	
NPI10 - Sum - median (IQR) [c)]	13 (3.5 - 22.5)	16 (6.5 - 25.5)	0.678
- mean (SD)	17.78 (16.75)	17.63 (14.09)	
PSMS - median (IQR) [c)]	18 (14.5 - 21.5)	19 (9 - 29)	0.329
- mean (SD)	17.25 (4.67)	18.14 (5.45)	
QoL-AD - patient's rating, mean (SD) [a)]	33.67 (5.03) n=46	34.38 (5.05) n=50	0.494
QoL-AD - caregivers' rating, mean (SD) [a)]	31.06 (5.57)	30.72 (5.05)	0.715
UPDRS - median (IQR) [c)]	2 (0 - 4)	3 (0.5 - 5.5)	0.117
- mean (SD)	3.08 (2.84)	4.38 (4.06)	
Weight - mean (SD) [a)]	66.46 (15.06) n=54	66.33 (11.78) n=58	0.958
Other psychotropic medication			
- median (IQR) c)	2 (1.5 - 2.5)	2 (1 - 3)	0.407
- mean (SD)	1.94 (1.01)	2.11 (1.11)	
Falls/day last 21 days before inclusion			
- median (IQR) [c)]	0 (0 - 0)	0 (0 - 0) n=64	0.820
- mean (SD)	0.02 (0.09)	0.01 (0.03)	

Mg oxazepam/day last 21 days before inclusion			
- median (IQR) [c)]	0 (0 - 0)	0 (0 - 0)	0.831
- mean (SD)	0.67 (3.63)	0.18 (0.55)	

ADG = Antidepressant Discontinuation Group, ACG = Antidepressant Continuation Group, SD = Standard Deviation, IQR = Interquartile Range, AD = Alzheimer's Disease, VaD = Vascular Dementia, CDR = Clinical Dementia Rating Scale, SIB = Severe Impairment Battery, CSDD = the Cornell Scale of Depression in Dementia, NPI10 = Neuropsychiatric Inventory 10 items version, PSMS = Lawton and Brody's Physical Self-Maintenance scale, QoL-AD = Quality of Life - Alzheimer Disease, UPDRS = Unified Parkinson's Disease Rating Scale, six-item version

[a)] Independent Student's t-test, [b)] Pearson Chi-square test [c)] Mann-Whitney U test

Table 1: Baseline characteristics

RESULTS

STUDY POPULATION

Patients were included from August 2008 to June 2010. A total of 205 patients were assessed for eligibility, 77 were excluded for various reasons, thus leaving 128 patients for randomization (see figure 1). Sixty-three patients were assigned to discontinuation of antidepressants and sixty-five were assigned to continuation with the antidepressants. Seventy-two patients (56%) used escitalopram, 47 patients (37%) citalopram, five patients (4%) sertraline and four patients (3%) paroxetine. There were no statistically significant differences between the two groups in terms of sex, age, CDR-score, dementia diagnosis, Cornell-score or NPI score at baseline (see table 1). The mean age was 85.3 years for the ADG and 86.1 years for the ACG. In the ADG and the ACG 77.8% and 72.3% were women, respectively. At baseline the ADG had a median CSDD score of four (Interquartile Range, IQR, 1.5 – 6.5), while the ACG had a median CSDD score of five (IQR 1.5 – 8.5). The median NPI-10 score was 13 (IQR 3.5 – 22.5) and 16 (IQR 6.5 – 25.5) for the ADG and the ACG, respectively.

A total of eleven patients (four in the ADG and seven in the ACG) were excluded from the efficacy analyses, either because no post-baseline assessments were available or because of study protocol violation, leaving 117 patients for the efficacy analysis. A total of 47 patients (36.7%) prematurely discontinued the study, 28 patients (44.4%) in the ADG and 19 patients (29.2%) in the ACG. The only

reason for drop out with significant difference between the two groups was increased neuropsychiatric symptoms, 13 patients (20.6%) in the ADG and four patients (6.2%) in the ACG (see table 3).

EFFICACY ANALYSES

The efficacy analyses are presented as intention-to-treat analysis (ITT) with the LOCF method and observed cases (OC) (see table 2).

Intention-to-treat analysis: The mean change between baseline and 25 weeks in the CSDD score was significantly different between the two groups, 2.53 (SD 5.61) in the ADG and - 0.43 (SD 3.61) in the ACG, p=0.001. When adjusted for baseline scores with Analysis of Covariance (ANCOVA) the differences in mean change in CSDD score between the groups were still significant; ADG 2.48 (SD 0.56) and ACG minus 0.38 (SD 0.56), p<0.001. The mean total score for the NPI-10 increased by 5.93 (SD 19.41) in the ADG and decreased by 1.39 (SD 15.26) in the ACG, p=0.023. Adjusting for baseline NPI-10 scores using ANCOVA, the change in NPI-10 score was 5.82 (SD 1.95) for the ADG and minus 1.27 (SD 1.98) for the ACG, p=0.012. Responses defined as a >30% increase or decrease on the CSDD were significantly different, as more patients in the ADG deteriorated than in the ACG, p=0.006.

Table 2. Results of the efficacy analysis at week 25

	ADG n = 59	ACG n = 58	p-value
Primary efficacy analysis			
Change in CSDD score, mean (SD) LOCF [a)]	2.53 (5.61) n=57	- 0.43 (3.61)	0.001*
Change in CSDD score, mean (SD) OC [a)]	0.52 (3.91) n=33	- 0.98 (3.63) n=46	0.085
Change in CSDD score, mean (SD) LOCF [c)]	2.48 (0.56) n=57	-0.38 (0.56)	< 0.001*
Change in NPI-10 score, mean (SD) LOCF [a)]	5.93 (19.41)	-1.39 (14.31) n=57	0.023*
Change in NPI-10 score, mean (SD) OC [a)]	0.80 (17.25) n=35	-1.59 (12.07) n=46	0.466
Change in NPI-10 score, mean (SD) LOCF [c)]	5.82 (1.95)	-1.27 (1.98)	0.012*
Secondary efficacy variables			
Change in CSDD mood score, mean (SD) [a)]	0.75 (1.85) n=53	-0.25 (1.85) n=51	0.006*
Change in CSDD non-mood score, mean (SD) [a)]	1.94 (5.16) n=55	0.42 (3.30) n=57	0.074
CSDD responders (%) [b)]			
> 30 % improvement	13 (22.0)	19 (32.8)	0.193
30 % improvement to 30 % deterioration	14 (23.7)	22 (37.9)	0.096
> 30 % deterioration	32 (54.2)	17 (29.3)	0.006*
Change in NPI – Affective subsyndrom, mean (SD) [a)]	1.59 (6.23)	- 0.69 (4.62)	0.026*
NPI - Affective subsyndrom, responders (%) [b)]			
> 30 % improvement	18 (30.5)	18 (31.0)	0.951
30 % improvement to 30 % deterioration	28 (47.5)	34 (58.6)	0.226
> 30 % deterioration	13 (22.0)	6 (10.3)	0.087
Change in NPI - agitation subsyndrom, mean (SD) [a)]	1.98 (7.80)	0.41 (7.39)	0.266
Change in NPI - psychotic subsyndrom - mean (SD) [a)]	1.07 (5.58)	0.09 (3.04)	0.240
Change in NPI - apathy - mean (SD) [a)]	0.73 (3.90)	-0.12 (3.58) n=57	0.224
Clinical Dementia Rating [b)]			
Missing (%)	3 (5.1)	7 (12.1)	0.177
CDR = 0.5 (%)	0 (0.0)	1 (1.7)	0.311
CDR = 1 (%)	6 (10.2)	7 (12.1)	0.744
CDR = 2 (%)	23 (39.0)	19 (32.8)	0.483
CDR = 3 (%)	27 (45.8	24 (41.4)	0.633
Change in SIB - mean (SD) [a)]	-0.87 (14.74) n=31	-1.95 (17.41) n=39	0.784
Change in UPDRS, mean (SD) [a)]	0.50 (2.67) n=58	0.07 (2.73)	0.392
Change in PSMS, mean (SD) [a)]	0.89 (3.27) n=56	1.06 (2.69) n=53	0.777
Change in weight, mean (SD) [a)]	-1.51 (3.66) n=37	-0.04 (3.62) n=46	0.071
Change in QoL-AD - patient's rating - mean (SD) [a)]	-0.50 (5.04) n=28	0.24 (4.99) n=33	0.567

Change in QoL-AD - caregivers' rating - mean (SD) [a)]	-2.26 (5.19) n=54	-1.90 (5.20) n=52	0.725
Change in falls/day, mean (SD) [a)]	-0.01 (0.08) n=56	0.01 (0.03) n=53	0.055
Change in mg oxazepam/day, mean (SD) [a)]	0.40 (2.43) n=54	0.07 (0.34) n=54	0.336
Change in psychotropic medication, median (IQR)	0 (0-0) n=56	0 (0-0) n=54	0.190
- mean (SD)	-0.13 (0.605)	-0.20 (0.562)	

ADG = Antidepressant Discontinuation Group, ACG = Antidepressant Continuation Group, CSDD = the Cornell Scale of Depression in Dementia, LOCF = last observation Carried Forward, OC = Observed Cases, SD = Standard Deviation, IQR = Interquartile Range, NPI-10 = the Neuropsychiatric Inventory 10 items version, CDR = the Clinical Dementia Rating Scale, SIB = Severe Impairment Battery, QoL-AD = Quality of Life - Alzheimer Disease, UPDRS=Unified Parkinson's Disease Rating Scale, six-item version, PSMS = Lawton's Physical Self-Maintenance scale

[a)] Independent Student's t-test, [b)] Pearson Chi-square test [c)] Analyze of Covariance, with baseline values as covariate, * $p<0.05$

Table 2: Differences at 25 weeks

The mean changes in score on the mood-CSDD subscale were 0.75 (SD 1.85) in the ADG and -0.25 (SD 1.85) in the ACG, p=0.006. No statistically significant difference between the mean change in the non-mood-CSDD score between the groups was found, p=0.074.

The mean change from baseline to twenty-five weeks for the NPI affective subsyndrom in the ADG and the ACG was 1.59 (SD 6.23) and -0.69 (SD 4.62) respectively, p=0.026. There were no statistically significant differences in the mean change between the groups in the NPI-Apathy sub item, p=0.224, the NPI-Agitation subsyndrom, p=0.266, or the NPI-psychosis subsyndrom, p=0.240. Neither of the other secondary endpoints differed significantly between the groups.

Observed cases: The mean change in total CSDD score between baseline and twenty-five weeks was 0.52 (SD 3.91) for the ADG and -0.98 (SD 3.63) for the ACG, p=0.085, while the mean change in the NPI-10 score was 0.80 (SD 17.25) for the ADG and -1.59 (SD 12·07) for the ACG, p= 0.466.

TOLERABILITY AND SAFETY

There was no statistically significant differences between the groups in the change in UPDRS score between baseline and week 25, ADG 0.50 (SD 2.67) and ACG 0.07 (SD 2.73), p=0.392.

Twenty-eight patients (44.4%) in the ADG discontinued the study prematurely for different reasons and nineteen patients (29.2%) in the ACG (see table 3). Thirteen patients in the ADG (20.6%) and four patients in the ACG (6.2%) discontinued the study prematurely due to increased depressive or neuropsychiatric symptoms, a statistically significant difference, p=0.019.

Table 3. Number of patients completing twenty-five weeks intervention and number of patients discontinued intervention prematurely

	ADG n = 63	ACG n = 65	p-value
Completed 25 weeks intervention, no (%) [1)]	35 (55.6)	46 (70.8)	0.074
Discontinued intervention, no (%)			
Death, somatic disease or hospitalization [2)]	7 (11.1)	7 (10.8)	1.000
Withdrawal of consent [2)]	5 (7.9)	4 (6.2)	0.742
Increased symptoms [2)]	13 (20.6)	4 (6.2)	0.019*
Could not swallow the study capsules [2)]	2 (3.2)	1 (1.5)	0.616
Moved from the nursing home [2)]	1 (1.6)	1 (1.5)	1.000
Did not take the study medication as prescribed [2)]	0 (0.0)	2 (3.1)	0.496

ADG = Antidepressant Discontinuation Group, ACG = Antidepressant Continuation Group

[1)] Pearson Chi-square test [2)] Fisher's Exact test, * p<0.05

Table 3: The drop-out rate

DISCUSSION

We have published the first antidepressant discontinuation RCT in patients with dementia. Previous studies on antidepressants for NPS in dementia have reported against antidepressants, and our hypothesis was that discontinuing antidepressants would not change the patient's depressive

symptoms.[25] Patients in the ADG had a statistically significant deterioration in their depressive symptoms compared to patients in the ACG, a deterioration demonstrated in the total CSDD score, the total score of the NPI-10, the mood subscore of the CSDD, the affective subscore of the NPI, and the response analyses (worsening or improving by more than 30%). None of the differences in secondary endpoints were statistically significant between the two groups. This effect of antidepressant over placebo on depressive symptoms in non-depressed patients with Alzheimer Disease and/or Vascular Dementia has to our knowledge never been demonstrated in a discontinuation study before.

Some caution should be taken in the interpretation of our study as our cohort is different from previous studies. In our study patients should not have depressive disorder according to ICD-10 criteria neither at inclusion or documented in their medical record, while RCT starting antidepressants often includes patients with a depressive disorder. All the patients with a depressive disorder documented in their medical record were excluded from the present study. Four patients (6.6%) in the ACG and seven patients (10.9%) in the ADG had a CSDD score above thirteen at baseline, which could indicate a severe depression.[20] They were nevertheless judged not to have a depressive disorder at inclusion. Although the indication for antidepressiva treatment is unclear for patients enrolled in our study, most of them have been prescribed antidepressant for depressive symptoms or apathy following their dementia. The last years focus on cerebrovascular side effects of antipsychotics have reduced the prescription of antipsychotics for NPS in Norway, and more patients could have been prescribed antidepressant for NPS. This is important remarks when interpreting the results. The aim of our study was to evaluate the effect of antidepressant on depressive symptoms and NPS, and care was taken to ensure that the enrolled patients did not suffer from a depressive disorder. As the patients experienced worsening of depressive symptoms after discontinuation, we conclude that antidepressants are effective for treating depressive symptoms in demented patients. In the ADG mean CSDD score increased from 5.03 to 7.56, which still is under the cut off score that is

usually used to define a possible depressive disorder in demented patients.[18,20] The mean change of 2.53 is a 50.3% worsening from baseline, but is it clinically significant? No statistically significant change was on QoL, ADL-function or side effects.

Our findings are supported by the previous RCTs on the effect of antidepressants on NPS of dementia, who have demonstrated an effect in favour of antidepressants over a placebo on emotional bluntness, anxiety, depressive mood and restlessness in patients with Alzheimer Disease (AD),[26] a favourable effect on behavioural symptoms in patients with AD,[6] and a decreased frequency of irritability and apathy in patients with AD.[27] Previous RCTs have also demonstrated that antidepressants are as effective in reducing agitation in dementia as haloperidol[28] and antidepressants have a similar effect to risperidone on behavioural symptoms and psychosis.[29] The favourable effect of antidepressants on depression has also been demonstrated on patients with AD and severe depression,[30] but a meta analysis of the effect of antidepressants on depression in patients with dementia concludes that the evidence in favour of using antidepressants in treating depression in patients with dementia is weak.[10]

The strength of our study is the multicenter randomized double blind placebo controlled design, which controls for all covariate variables. We used internationally recommended assessment tools, and the follow-up time was twenty-five weeks. The study was monitored by independent monitoring nurses. We used LOCF to impute missing values, which is a questionable technique. In our opinion LOCF is a conservative imputing technique in a discontinuation study, as most of the patients who discontinued intervention had worsening depressive symptoms. An imputing technique considering the worsening trend in the symptoms would artificially increase the difference between the two study groups. The findings in our study were confirmed by two different assessment tools, which strengthen the study. The weakness of our study is the high drop-out rate, only 63·3% of included patients completed the twenty-five week study period. However, drop outs because of increased

NPS were more common in the ADG group, which could be a contraindication for the withdrawal of antidepressants. This could also explain why no statistical differences between the two groups were found using the Observed Cases analyses. The study involved many research nurses, which could bias the data even though each research nurse had completed a one-day course. The discontinuation of the antidepressants over one week is fairly quick, and some of the patients may have experienced discontinuation symptoms rather than increased depressive symptoms. However, after twenty-five weeks discontinuation symptoms should not be present any more.

Conclusion

After 25 weeks, there was a statistically significant difference between the two groups, where the ADG had increased depressive symptoms and the ACG had a small decrease in their depressive symptoms.

Contributors

SB, GS, and KE participated in design of the study. SB was principal study investigator. All authors participated in analysis and interpretation of results. SB drafted the manuscript. All authors participated in critical revision of the article for intellectual content and approved the final version of the manuscript for publication

Conflicts of interest

SB none; GS none; KE none.

Acknowledgement:

The study was funded by unrestricted grants from the Innlandet Hospital Trust, the Research Council of Norway and the South-Eastern Norway Regional Health Authority. H. Lundbeck A/S provided the

study with escitalopram tablets and placebos free of charge (56% of the patients), but with no obligations for publication.

Protocol

A full trial protocol can be accessed at http://www.sykehuset-innlandet.no/omoss/avdelinger/alderpsykiatrisk-forskningssenter/prosjekter/Sider/desep.aspx

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